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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 213/55, 213/56, 213/81, 213/82, 401/12, 405/12, A61K 31/44

A1

(11) International Publication Number: WO 97/47599

(43) International Publication Date: 18 December 1997 (18.12.97)

(21) International Application Number: PCT/JP97/02004

(22) International Filing Date: 11 June 1997 (11.06.97)

(30) Priority Data:
PO0482 14 June 1996 (14.06.96) AU

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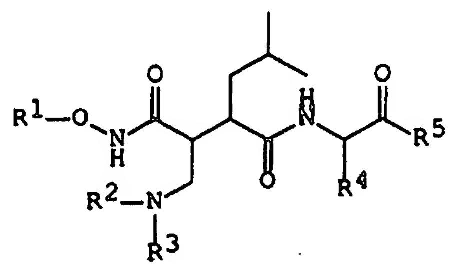
(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

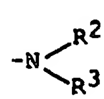
(54) Title: SUCCINAMIDE DERIVATIVES USEFUL AS TNF- AND/OR MMP INHIBITORS

(57) Abstract

A compound of formula (I), in which R^1 is hydrogen or hydroxy-protective group, R^2 is hydrogen or acyl, R^3 is hydrogen or lower alkyl, or the formula (II) is (III), R^4 is heterocyclic (lower) alkyl, and R^5 is lower alkoxy or lower alkylamino, or a pharmaceutically acceptable salt thereof, which is useful as a medicament.



(I)



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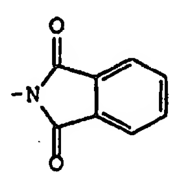

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DESCRIPTION

SUCCINAMIDE DERIVATIVES USEFUL AS TNF- AND/OR MMP INHIBITORS

TECHNICAL FIELD

The present invention relates to new compound and pharmaceutically acceptable salts thereof.

More particularly, it relates to new compound and pharmaceutically acceptable salts thereof which are useful as inhibitors of matrix metalloproteinases (heteinafter to be referred to as MMP) or the production of tumor necrosis factor α (hereinafter to be referred to as TNF α), to a pharmaceutical composition comprising the same, to use of the same as a medicament, and to a method for using the same therapeutically in the treatment and/or the prevention of MMP or TNF α mediated diseases.

One object of the present invention is to provide new and useful compounds and pharmaceutically acceptable salts thereof which have pharmacological activities such as MMP or TNF α inhibitory activity and the like.

Another object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said compound or a pharmaceutically acceptable salt thereof.

A further object of the present invention is to provide use of said compounds and pharmaceutically acceptable salts thereof as a medicament for prophylactic and therapeutic treatment of MMP or TNF α mediated diseases.

A still further object of the present invention is to provide a method for using the same for the treatment and/or the prevention of MMP or TNF α mediated diseases in mammals, especially humans.

The compounds of the present invention have inhibitory activity on MMP or the production of TNF α, and

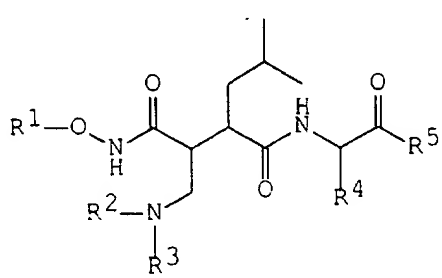
are useful in the treatment and/or prevention of a disease such as stroke, arthritis, cancer, tissue ulceration, decubitus ulcer, restenosis, periodontal disease, epidermolysis bullosa, scleritis, psoriasis and other diseases characterized by matrix metalloproteinase activity, as well as AIDS, sepsis, septic shock and other diseases caused by the production of TNF α.

There are a number of enzymes which effect the breakdown of structural proteins and which are structurally related metalloproteases. Matrix-degrading metalloprotease, such as gelatinase (MMP-2, MMP-9), stromelysin (MMP-3) and collagenase (MMP-1), are involved in tissue matrix degradation and have been implicated in many pathological conditions involving abnormal connective tissue and basement membrane matrix matabolism, such as arthritis (e.g., osteoarthritis and rheumatoid arthritis), tissue ulceration (e.g., corneal, epidermal and gastric ulceration), abnormal wound healing, periodonal disease, bone disease (e.g., Paget's disease and osteoporosis), tumor matastasis or invasion as well as HIV-infection.

Tumor necrosis factor is recognized to be involved in many infections and autoimune diseases. Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock.

DISCLOSURE OF INVENTION

The object compound of the present invention can be represented by the following general formula :

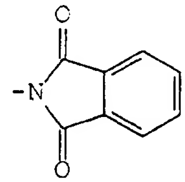


(I)

in which R^1 is hydrogen or hydroxy-protective group,

R^2 is hydrogen or acyl,

R^3 is hydrogen or lower alkyl, or

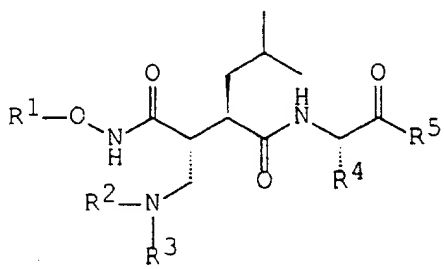
the formula : $-N\begin{matrix}R^2\\R^3\end{matrix}$ is  ,

R^4 is heterocyclic(lower)alkyl, and

R^5 is lower alkoxy or lower alkylamino,

or pharmaceutically acceptable salts thereof.

Further, the compound (I) having the most potent activities can be represented by the following configuration.

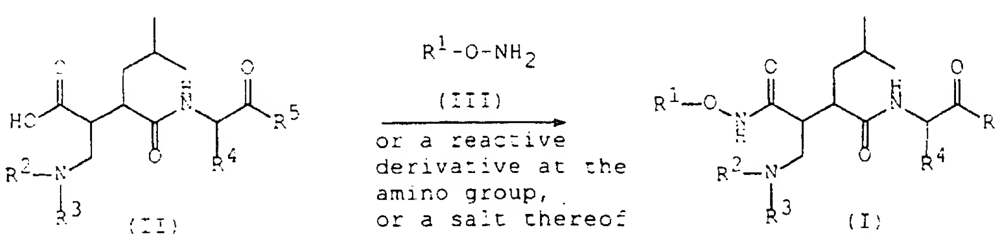


(IA)

in which R^1, R^2, R^3, R^4 and R^5 are each as defined above.

According to the present invention, the new compound (I) and salts thereof can be prepared by the processes as shown in the following schemes.

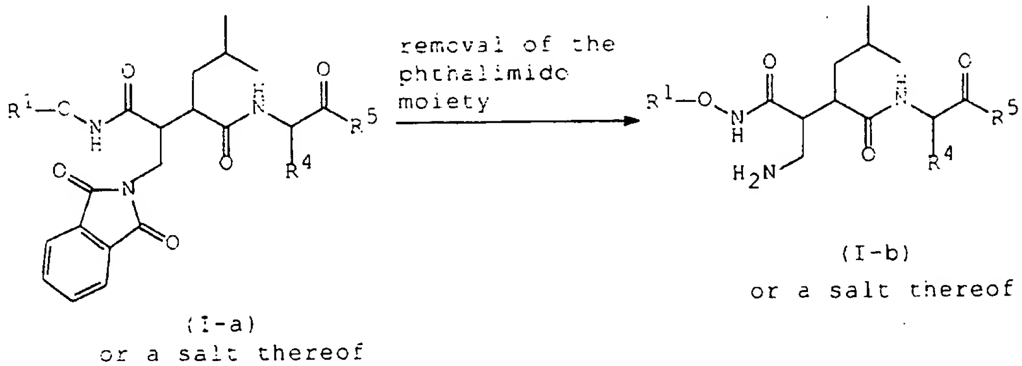
<u>Process 1</u> :



or a reactive derivative at the carboxy group, or a salt threof

or a salt thereof

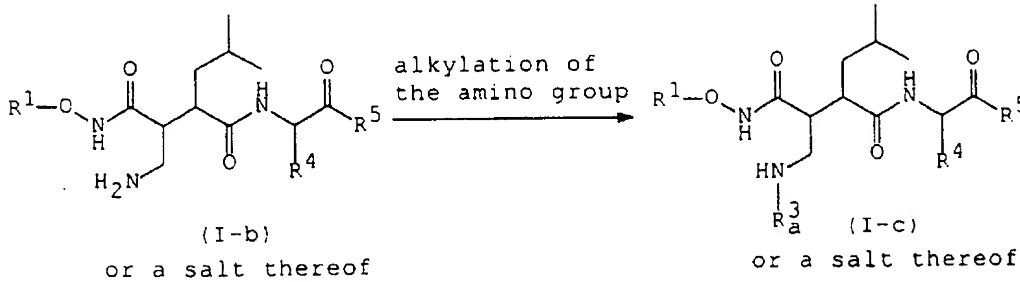
Process 2 :



(I-a) or a salt thereof

(I-b) or a salt thereof

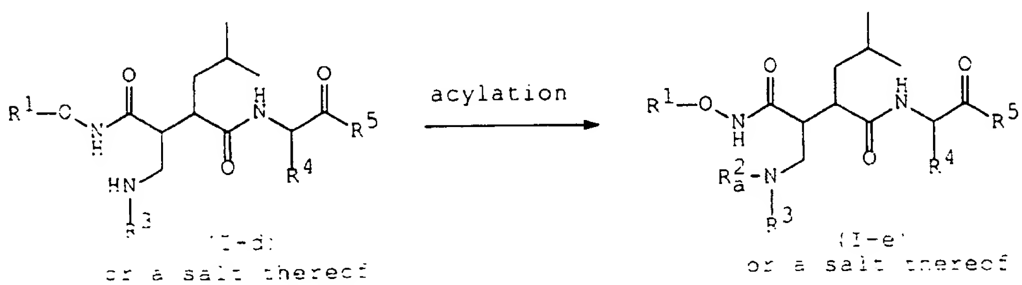
Process 3



(I-b) or a salt thereof

(I-c) or a salt thereof

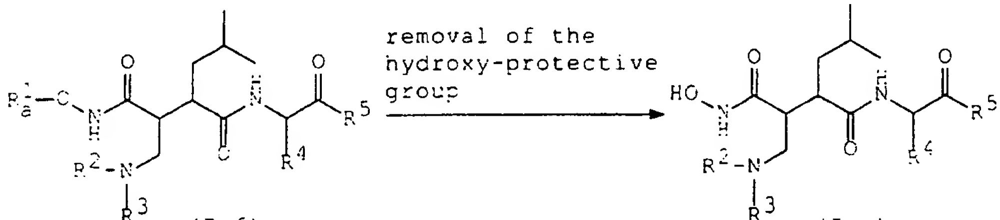
Process 4



(I-d) or a salt thereof

(I-e) or a salt thereof

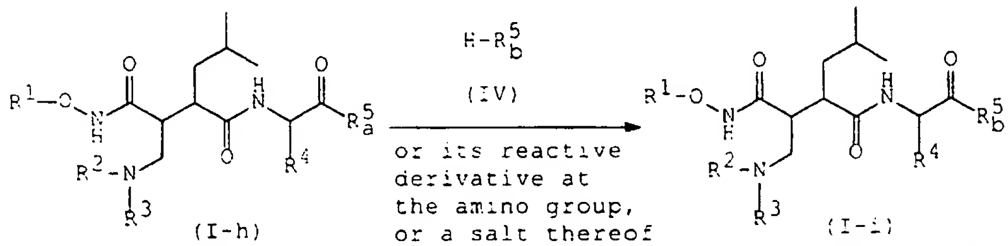
Process 5



(I-f) or a salt thereof

(I-g) or a salt thereof

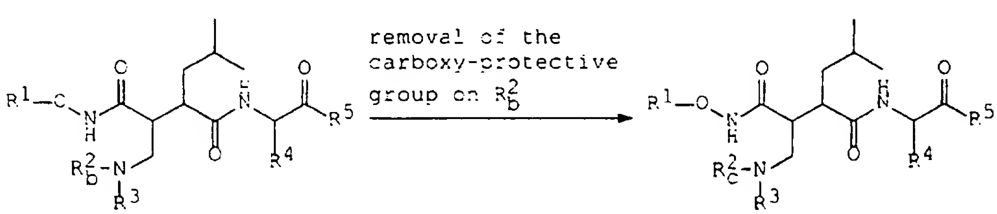
Process 6



(I-h) or a salt thereof

(I-i) or a salt thereof

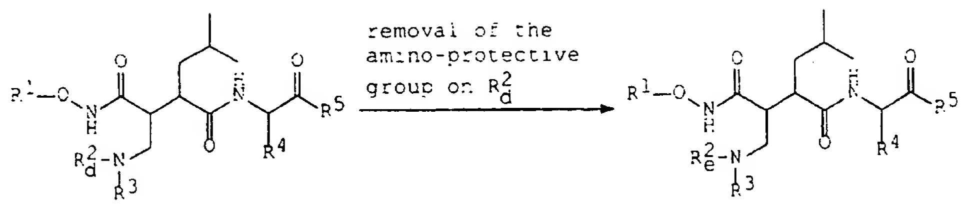
Process 7



(I-j) or a salt thereof

(I-k) or a salt thereof

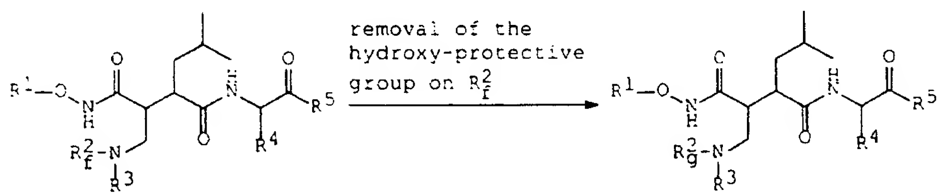
Process 8



(I-l) or a salt thereof

(I-m) or a salt thereof

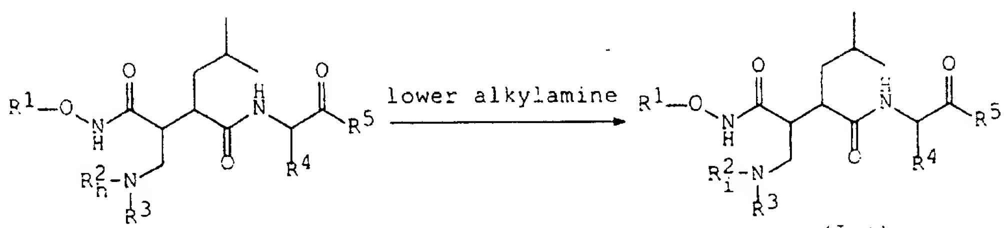
Process 9



(I-n) or a salt thereof

(I-o) or a salt thereof

Process 10



(I-p) or a salt thereof

(I-q) or a salt thereof

in which R^1, R^2, R^3, R^4 and R^5 are each as defined above,

R^1_a is hydroxy-protective group,

R^2_a is acyl,

R^2_b is protected carboxy(lower)alkanoyl,

R^2_c is carboxy(lower)alkanoyl,

R^2_d is protected amino(lower)alkoxycarbonyl, protected amino(lower)alkanoyl, lower alkanoyl substituted by protected amino and hydroxy, or N-protected imidazolidinyl optionally substituted by oxo,

R^2_e is amino(lower)alkoxycarbonyl, amino(lower)alkanoyl, lower alkanoyl substituted by amino and hydroxy, or imidazolidinyl optionally substituted by oxo,

R^2_f is protected hydroxy(lower)alkoxycarbonyl, or protected hydroxy(lower)alkanoyl,

R^2_g is hydroxy(lower)alkoxycarbonyl, or hydroxy(lower)alkanoyl,

R^2_h is lower alkoxycarbonyl(lower)alkylcarbamoyl or lower alkoxycarbonyllower alkanoyl,

R^2_i is lower alkylcarbamoyl(lower)alkylcarbamoyl or lower alkylcarbamoyl(lower)alkanoyl,

R^3_a is lower alkyl,

R^5_a is lower alkoxy, and

R^5_b is lower alkylamino.

The starting compound (II) used in the Process 1 may be new and can be prepared by the following Preparations or by a conventional manner.

Suitable pharmaceutically acceptable salts of the object compound (I) may be a conventional non-toxic salt and include an acid addition salt such as an organic acid

salt (e.g. acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydriodide, sulfate, nitrate, phosphate, etc.), or a salt with a base such as an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), an alkali metal salt (e.g. sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), or the like.

The object compound (I) and pharmaceutically acceptable salts thereof may include a solvate [e.g., enclosure compound (e.g., hydrate, etc.)].

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention includes within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 (or 2 to 6 for lower alkenyl group), preferably 1 to 4 carbon atoms (or 2 to 4 carbon atoms for the same), and the term "higher" is intended to mean more than 6, preferably 7 to 12 carbon atoms, unless otherwise indicated.

Suitable "hydroxy-protective group" may include a common one, for example, acyl as mentioned below, ar(lower)alkyl such as mono- or di- or triphenyl(lower)alkyl (e.g. benzyl, benzhydryl, trityl, phenethyl, naphthylmethyl, etc.), etc.; trisubstituted silyl such as tri(lower)alkylsilyl (e.g. trimethylsilyl, triethylsilyl, isopropyldimethylsilyl, t-butyldimethylsilyl, diisopropylmethylsilyl, etc.), triarylsilyl (e.g. triphenylsilyl, etc.), triar(lower)alkylsilyl (e.g. tribenzylsilyl, etc.), etc.;

and the like.

Preferable "hydroxy-protective group" thus defined may be C_6-C_{10} aroyl, C_6-C_{10} ar(lower)alkyl and lower alkanoyl, and the most preferable one may be benzyl.

Suitable "acyl" may include an aliphatic acyl, an aromatic acyl, a heterocyclic acyl and an aliphatic acyl substituted with aromatic or heterocyclic group(s) derived from acids such as carboxylic, carbonic, carbamic, sulfonic acids, wherein said heterocyclic group(s) may be the same as those mentioned below.

The aliphatic acyl may include saturated or unsaturated, acyclic or cyclic ones, such as carbamoyl, oxamoyl, lower alkanoyl optionally substituted by halogen (e.g. chloro, fluoro, iodo, bromo, etc.) (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, trifluoroacetyl, etc.), lower alkanesulfonyl (e.g. mesyl, ethanesulfonyl, propanesulfonyl, etc.), lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, t-butoxycarbonyl, etc.), lower alkenoyl (e.g. acryloyl, methacryloyl, crotonoyl, etc.), (C_3-C_7)cycloalkanecarbonyl (e.g. cyclopropanecarbonyl, cyclobutanecarbonyl, cyclohexanecarbonyl, etc.), (C_3-C_7)cycloalkyl(lower)-alkanoyl (e.g. cyclohexylacetyl, etc.), amidino, protected carboxycarbonyl such as lower alkoxalyl (e.g. methoxalyl, ethoxalyl, t-butoxalyl, etc.), mono- or di(lower)alkyl-amino(lower)alkanoyl (e.g. dimethylaminoacetyl, etc.); lower or higher alkylcarbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, t-butylcarbamoyl, 2-methylbutylcarbamoyl, pentylcarbamoyl, hexylcarbamoyl, heptylcarbamoyl, octylcarbamoyl, nonylcarbamoyl, etc.), di(lower)alkylcarbamoyl (e.g. dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, diisopropylcarbamoyl,

dibutylcarbamoyl, diisobutylcarbamoyl, dihexylcarbamoyl, etc.), C_3-C_7 cycloalkylcarbamoyl (e.g. cyclopropylcarbamoyl, cyclobutylcarbamoyl, cyclopentylcarbamoyl, cyclohexylcarbamoyl, cycloheptylcarbamoyl, etc.), N-lower alkyl-N-(C_3-C_7)-cycloalkylcarbamoyl (e.g. N-methyl-N-cyclopropylcarbamoyl, N-methyl-N-cyclohexylcarbamoyl, N-ethyl-N-cyclohexylcarbamoyl, N-propyl-N-cyclohexylcarbamoyl, etc.), di(C_3-C_7)cyclohexylcarbamoyl (e.g. dicyclopropylcarbamoyl, dicyclopentylcarbamoyl, dicyclohexylcarbamoyl, etc.), N-[di(lower)alkylcarbamoyl(C_3-C_7)cycloalkyl]carbamoyl [e.g. N-(1-dimethylcarbamoylcyclohexyl)carbamoyl, etc.], N-[di(lower)alkylcarbamoyl(lower)alkyl(C_3-C_7)cycloalkyl]-carbamoyl [e.g. N-[1-(dimethylcarbamoylmethyl)cyclohexyl]-carbamoyl, etc.], N-[carbamoyl(lower)alkyl]carbamoyl [e.g. N-[1-carbamoyl]-2-methylbutyl]carbamoyl, etc.], N-[(lower)alkylcarbamoyl(lower)alkyl]carbamoyl [e.g. N-(methylcarbamoylmethyl)carbamoyl, N-(1-isopropylcarbamoyl-2-methylbutyl)carbamoyl, etc.], N-[N,N-lower alkylenecarbamoyl(lower)alkyl]carbamoyl [e.g. N-[2-methyl-1-(piperidinocarbonyl)butyl]carbamoyl, etc.], N-[N,N-di(lower)alkylcarbamoyl(lower)alkyl]carbamoyl [e.g. N-(dimethylcarbamoylmethyl)carbamoyl, N-[1-(dimethylcarbamoyl)ethyl]carbamoyl, N-[1-(dimethylcarbamoyl)-2-methylpropyl]carbamoyl, N-[2,2-dimethyl-1-(dimethylcarbamoyl)propyl]carbamoyl, N-[2-methyl-1-(dimethylcarbamoyl)butyl]carbamoyl, N-[2-methyl-1-(diethylcarbamoyl)butyl]carbamoyl, N-[3-methyl-1-(dimethylcarbamoyl)butyl]carbamoyl, N-(1-dimethylcarbamoylpentyl)carbamoyl, etc.], N-(lower)alkyl-N-[N,N-di(lower)alkylcarbamoyl](lower)-alkylcarbamoyl [e.g. N-methyl-N-[1-dimethylcarbamoyl-2-methylbutyl]carbamoyl, N-methyl-N-[1-dimethylcarbamoyl-3-methylbutyl]carbamoyl, etc.], and the like.

The aromatic acyl may include C_6-C_{10} aroyl (e.g. benzoyl, toluoyl, xyloyl, etc.), C_6-C_{10} arenesulfonyl (e.g. benzenesulfonyl, tosyl, etc.), C_6-C_{10} arylcarbamoyl (e.g. phenylcarbamoyl, etc.), C_6-C_{10} aryloxalyl (e.g. phenyloxalyl, etc.), and the like.

The heterocyclic acyl may include heterocycliccarbonyl such as furoyl, thenoyl, nicotinoyl, isonicotinoyl, oxolanecarbonyl optionally substituted by oxo (e.g. 2-oxo-5-oxolanecarbonyl, etc.), thiazolylcarbonyl, thiadiazolylcarbonyl, indolylcarbonyl, isoindolylcarbonyl, tetrazolylcarbonyl, morpholinocarbonyl, pyrrolylcarbonyl, pyrazinylcarbonyl, thiomorpholinocarbonyl, pyridinecarbonyl optionally substituted by lower alkyl [e.g. 2-(or 3- or 4-)-pyridinecarbonyl, 6-methyl-2-pyridinecarbonyl, 2-methyl-5-pyridinecarbonyl, etc.], quinolinecarbonyl optionally substituted by hydroxy (e.g. 2-quinolinecarbonyl, 3-quinolinecarbonyl, 4-hydroxy-2-quinolinecarbonyl, etc.), lower alkyleneaminocarbonyl optionally substituted by oxo (e.g. aziridin-1-ylcarbonyl, azetidin-1-ylcarbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, hexahydro-1H-azepin-1-ylcarbonyl, octahydroazocin-1-ylcarbonyl, tetrahydroquinolinecarbonyl, tetrahydroisoquinolinecarbonyl, dihydropyridinecarbonyl, tetrahydropyridinecarbonyl, 2-oxo-5-pyrrolidinecarbonyl, 2-oxo-4-imidazolidinecarbonyl, etc.), heterocycliccarbamoyl such as pyridylcarbamoyl (e.g. 4-pyridylcarbamoyl, etc.), piperidylcarbamoyl, etc. and the like.

The aliphatic acyl substituted with aromatic group(s) may include (C_6-C_{10})ar(lower)alkanoyl such as phenyl(lower)alkanoyl (e.g. phenylacetyl, phenylpropionyl, phenylhexanoyl, etc.), (C_6-C_{10})ar(lower)alkoxycarbonyl such as phenyl(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.),

(C_6-C_{10})aryloxy(lower)alkanoyl such as phenoxy(lower)alkanoyl (e.g. phenoxyformyl, phenoxyacetyl, phenoxypropionyl, etc.), ar(lower)alkoxalyl such as phenyl(lower)alkoxalyl (e.g. benzyloxalyl, etc.), ar(lower)alkenoyl such as phenyl(lower)alkenoyl (e.g. cinnamoyl, etc.), ar(lower)alkylsulfonyl (e.g. benzylsulfonyl, etc.), and the like.

The aliphatic acyl substituted with heterocyclic group(s) may include heterocyclic(lower)alkanoyl such as thienyl(lower)alkanoyl, imidazolyl(lower)alkanoyl (e.g. 4-imidazolylacetyl, etc.), furyl(lower)alkanoyl, tetrazolyl(lower)alkanoyl, thiazolyl(lower)alkanoyl, thiadiazolyl(lower)alkanoyl, pyridyl(lower)alkanoyl [e.g. pyridin-3-ylacetyl, 3-(pyridin-3-yl)propionyl, etc.], lower alkyleneamino(lower)alkanoyl (e.g. 3-(piperidin-1-yl)propionyl, etc.), etc.; heterocyclic(lower)alkylcarbamoyl, such as pyridyl(lower)alkylcarbamoyl, etc.; and the like.

These acyl groups may be further substituted with one or more, preferably one to three suitable substituents such as carboxy, lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, etc.), halogen, (e.g. chlorine, bromine, iodine, fluorine), carbamoyl, mono- or di(lower)alkylcarbamoyl (e.g. methylcarbamoyl, etc.), amino, protected amino such as lower alkanoylamino (e.g. formamido, acetamido, propionamido, etc.), and lower alkoxycarbonylamino (e.g. t-butoxycarbonylamino, etc.), mono- or di(lower)alkylamino (e.g. dimethylamino, etc.), lower alkoxycarbonylamino (e.g. t-butoxycarbonylamino, etc.), lower alkylsulfonyl (e.g. methylsulfonyl, etc.), arylsulfonyl (e.g. phenylsulfonyl, tosyl, etc.), ar(lower)alkyl (e.g. benzyl, etc.), hydroxy, lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, etc.), carboxy, protected carboxy as mentioned below such as lower alkoxycarbonyl (e.g. methoxycarbonyl,

etc.), carboxy(lower)alkyl (e.g. carboxymethyl, carboxyethyl, etc.), protected carboxy(lower)alkyl (e.g. t-butoxycarbonylmethyl, etc.), lower alkanoyloxy (e.g. acetoxy, etc.), lower alkoxycarbonyl (e.g. methoxycarbonyl, etc.), amino- or imino-protective group such as acyl (e.g. benzyloxycarbonyl, etc.), and the like.

Preferable acyl thus defined may be :

- lower alkanoyl (e.g. acetyl, propionyl, etc.);
- di(lower)alkylcarbamoyl (e.g. dimethylcarbamoyl, etc.);
- C_6-C_{10} aroyl (e.g. benzoyl, etc.);
- C_6-C_{10} arylcarbamoyl (e.g. phenylcarbamoyl, etc.);
- heterocyclecarbonyl such as pyridinecarbonyl optionally substituted by lower alkyl [e.g. 2-(or 3- or 4-)pyridinecarbonyl, 3-methyl-2-pyridinecarbonyl, 4-methyl-3-pyridinecarbonyl, etc.]; quinolinecarbonyl optionally substituted by hydroxy (e.g. 2-quinolinecarbonyl, 3-quinolinecarbonyl, 4-hydroxy-2-quinolinecarbonyl, etc.); etc.;
- lower alkyleneaminocarbonyl (e.g. pyrrolidin-1-ylcarbonyl, etc.);
- heterocyclic(lower)alkanoyl such as pyridyl(lower)alkanoyl [e.g. pyridin-3-ylacetyl, 3-(pyridin-3-yl)propionyl, etc.); etc.;
- lower alkanoyl substituted by mono- or di(lower)alkylamino (e.g. dimethylaminoacetyl, etc.); and the like;

wherein said heterocyclic group may be saturated or unsaturated 3- to 8-membered (preferably 5- or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), or unsaturated 7- to 12-membered condensed (preferably bicyclic) heterocyclic group containing 1 to 4 nitrogen atom(s).

Another preferable acyl thus defined may be :

(1) oxamoyl;

(2) lower alkanoyl (e.g. acetyl, propionyl, isobutyryl, pivaloyl, etc.) optionally substituted by halogen (e.g. trifluoroacetyl, etc.);

(3) lower alkanesulfonyl (e.g. mesyl, ethanesulfonyl, etc.);

(4) lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, isopropoxycarboyl, isobutoxycarbonyl, t-butoxycarbonyl, etc.);

(5) (C_3-C_7)cycloalkanecarbonyl (e.g. cyclopropanecarbonyl, etc.);

(6) di(lower)alkylamino(lower)alkanoyl (e.g. dimethylaminoacetyl, etc.);

(7) lower alkylcarbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, isopropylcarbamoyl, t-butylcarbamoyl, etc.);

(8) di(lower)alkylcarbamoyl (e.g. dimethylcarbamoyl, etc.);

(9) N-[(lower)alkylcarbamoyl(lower)alkyl]carbamoyl (e.g. N-(methylcarbamoylmethyl)carbamoyl, etc.);

(10) C_6-C_{10} aroyl (e.g. benzoyl, etc.);

(11) C_6-C_{10} arenesulfonyl (e.g. benzenesulfonyl, etc.);

(12) C_6-C_{10} arylcarbamoyl (e.g. phenylcarbamoyl, etc.);

(13) heterocyclic-carbonyl optionally substituted by the group consisting of acyl such as C_6-C_{10} ar(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, etc.), lower alkyl (e.g. methyl, etc.), hydroxy and oxo; said heterocyclic group being

unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, azepinyl (e.g. 1H-azepinyl, etc.), pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, dihydropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

saturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, perhydroazepinyl (e.g. perhydro-1H-azepinyl, etc.), pyrrolidinyl, imidazolidinyl, piperidinyl (e.g. piperidino, etc.), piperazinyl, etc.;

unsaturated 7- to 12-membered (more preferably 9- or 10- membered) condensed (preferably bicyclic) heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom, for example, furyl, etc.;

saturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom, for example, oxolanyl, etc.; and the like, for example,

- pyrrolylcarbonyl (e.g. 2-pyrrolylcarbonyl, etc.);
- pyridinecarbonyl ([e.g. 2-(or 3- or 4-)pyridinecarbonyl, etc.) optionally substituted by lower alkyl (e.g. 6-methyl-2-pyridinecarbonyl, 2-methyl-5-pyridinecarbonyl, etc.);
- pyrazinylcarbonyl (e.g. pyrazin-2-ylcarbonyl, etc.);
- pyrrolidinylcarbonyl (e.g. pyrrolidin-1-ylcarbonyl, etc.) optionally substituted by oxo (e.g. 2-oxopyrrolidin-5-ylcarbonyl, etc.);
- imidazolizinylcarbonyl optionally substituted by the group consisting of oxo and C_6-C_{10} ar(lower)-alkoxycarbonyl (e.g. 2-oxo-4-imidazolizinecarbonyl, 1-benzyloxycarbonyl-2-oxo-4-imidazolidinecarbonyl, etc.);
- quinolinecarbonyl (e.g. 2-quinolinecarbonyl, 3-quinolinecarbonyl, etc.) optionally substituted by hydroxy (e.g. 4-hydroxy-2-quinolinecarbonyl, etc.);

- indolylcarbonyl; isoindolylcarbonyl;
- furoyl [e.g. 2-(or 3-)furylcarbonyl, etc.];
- oxolanecarbonyl optionally substituted by oxo (e.g. 2-oxo-5-oxolanecarbonyl, etc.); and the like;

(14) heterocyclic-carbamoyl; said heterocyclic group being

unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, azepinyl (e.g. 1H-azepinyl, etc.), pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, dihydropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

saturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, perhydroazepinyl (e.g. perhydro-1H-azepinyl, etc.), pyrrolidinyl, imidazolidinyl, piperidinyl (e.g. piperidino, etc.), piperazinyl, etc.;

unsaturated 7- to 12-membered (more preferably 9- to 10-membered) condensed (preferably bicyclic) heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom, for example, furyl, etc.;

saturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom, for example, oxolanyl, etc.; and the like, for example,

- pyridylcarbamoyl (e.g. 4-pyridylcarbamoyl, etc.); and the like;

(15) (C_6-C_{10})aryloxy(lower)alkanoyl such as phenoxy(lower)alkanoyl (e.g. phenoxyformyl, etc.); etc.;

(16) heterocyclic(lower)alkanoyl; said heterocyclic group being

unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, azepinyl (e.g. 1H-azepinyl, etc.), pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, dihydropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

saturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, perhydroazepinyl (e.g. perhydro-1H-azepinyl, etc.), pyrrolidinyl, imidazolidinyl, piperidinyl (e.g. piperidino, etc.), piperazinyl, etc.;

unsaturated 7- to 12-membered (more preferably 9- to 10-membered) condensed (preferably bicyclic) heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom, for example, furyl, etc.;

saturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom, for example, oxolanyl, etc.; and the like, for example,

- imidazolyl(lower)alkanoyl (e.g. 4-imidazolylacetyl, etc.);
- pyridyl(lower)alkanoyl [e.g. pyridin-3-ylacetyl, 3-

(pyridin-3-yl)propionyl, etc.);
- piperidinyl(lower)alkanoyl [e.g. 3-(piperidin-1-yl)propionyl, etc.];

(17) lower alkylcarbamoyl(lower)alkanoyl (e.g. methylcarbamoylacetyl, etc.);

(18) carboxy(lower)alkanoyl (e.g. carboxyacetyl, 3-carboxypropionyl, etc.);

(19) protected carboxy(lower)alkanoyl such as lower alkoxycarbonyl(lower)alkanoyl (e.g. ethoxycarbonylacetyl, etc.); etc.;

(20) hydroxy(lower)alkanoyl (e.g. hydroxyacetyl, 2,3-dihydroxypropionyl, 2,3,4,5,6-pentahydroxyhexanoyl, etc.);

(21) protected hydroxy(lower)alkanoyl such as lower alkanoyloxy(lower)alkanoyl (e.g. acetoxyacetyl, etc.); etc.;

(22) lower alkoxy(lower)alkanoyl (e.g. methoxyacetyl, etc.);

(23) lower alkoxy(lower)alkoxycarbonyl (e.g. 2-methoxyethoxycarbonyl, etc.);

(24) amino(lower)alkoxycarbonyl (e.g. 2-aminoethoxycarbonyl, etc.);

(25) protected amino(lower)alkoxycarbonyl such as C_6-C_{10} ar(lower)alkoxycarbonylamino(lower)alkoxycarbonyl (e.g. 2-(benzyloxycarbonylamino)ethoxycarbonyl, etc.);

(26) lower alkoxycarbonyl(lower)alkylcarbamoyl (e.g. methoxycarbonylmethylcarbamoyl, etc.);

(27) lower alkylsulfonyl(lower)alkanoyl (e.g. methylsulfonylacetyl, etc.);

(28) hydroxy(lower)alkoxycarbonyl (e.g. 2-hydroxyethoxycarbonyl. etc.);

(29) protected hydroxy(lower)alkoxycarbonyl such as lower alkanoyloxy(lower)alkoxycarbonyl (e.g. 2-acetoxyethoxycarbonyl, etc.); etc.;

(30) lower alkanoyl substituted by the group consisting of amino and hydroxy (e.g. 2-amino-3-hydroxypropionyl,

etc.);

(31) lower alkanoyl substituted by the group consisting of protected amino and hydroxy such as lower alkanoyl substituted by the group consisting of lower alkoxycarbonylamino and hydroxy (e.g. 2-t-butoxycarbonylamino-3-hydroxypropionyl, etc.); etc.;

(32) amino(lower)alkanoyl (e.g. aminoacetyl, etc.);

(33) protected amino(lower)alkanoyl such as lower alkanoylamino(lower)alkanoyl (e.g. acetamidoacetyl, etc.), lower alkoxycarbonylamino(lower)alkanoyl (e.g. t-butoxycarbonylaminoacetyl, etc.); etc.;

and the like.

Suitable "lower alkyl" or lower alkyl moiety may include, unless otherwise indicated, a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, and the like, in which the most preferred example may be methyl for R^3.

Suitable "lower alkoxy" or lower alkoxy moiety may include, unless otherwise indicated, a straight or branched one such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, hexyloxy, and the like, in which the most preferable example may be methoxy for R^5.

Preferable "heterocyclic(lower)alkyl" means lower alkyl substituted by heterocyclic group as mentioned below, in which more preferable heterocyclic group may be saturated or unsaturated 3- to 8-membered (preferably 5- or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), or

unsaturated 7- to 12-membered (more preferably 9- to 10-membered) condensed (preferably bicyclic) heterocyclic group containing 1 to 4 nitrogen atom(s), wherein preferable example of heterocyclic(lower)alkyl may be

pyridyl(lower)alkyl, and the most preferable one may be 2-pyridylmethyl and 4-pyridylmethyl.

Suitable "heterocyclic group" as mentioned above may include saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one hetero-atom such as oxygen, sulfur and nitrogen atom.

Preferable heterocyclic group may be

unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, azepinyl (e.g. 1H-azepinyl, etc.) pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, dihydropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

saturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, perhydroazepinyl (e.g. perhydro-1H-azepinyl, etc.), pyrrolidinyl, imidazolidinyl, piperidinyl (e.g. piperidino, etc.), piperazinyl, etc.;

unsaturated 7- to 12-membered (more preferably 9- to 10-membered) condensed (preferably bicyclic) heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

saturated 7- to 12-membered (more preferably 9- to 10-membered) condensed (preferably bicyclic) heterocyclic group containing 1 to 4 nitrogen atom(s), for example, 7-azabicyclo[2.2.1]heptyl, 3-azabicyclo[3.2.2]nonanyl, etc.;

unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 2 oxygen

atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

saturated 3- to 8-membered (more preferably 5- to 7-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl (e.g. morpholino, etc.), sydnonyl, etc.;

unsaturated 7- to 12-membered (more preferably 9- to 10-membered) condensed (preferably bicyclic) heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;

saturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;

unsaturated 7- to 12-membered (more preferably 9- to 10-membered) condensed (preferably bicyclic) heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s), for example, furyl, etc.;

saturated 3- to 8-membered (morepreferably 5- or 6-membered) heterocyclic group containing 1 to 2 oxygen atom(s), for example, oxolanyl, etc.;

unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl,

etc.;

unsaturated 7- to 12-membered (more preferably 9- to 10-membered) condensed (preferably bicyclic) heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc.;

unsaturated 7- to 12-membered (more preferably 9- to 10-membered) condensed (preferably bicyclic) heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc., and the like.

Suitable "lower alkylamino" may include conventional one such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, pentylamino, hexylamino, and the like, in which more preferable example may be C_1-C_4 alkylamino and the most preferable one may be methylamino.

Preferable Examples of R^1, R^2, R^3, R^4 and R^5 are as follows :

R^1 is hydrogen,
R^2 is hydrogen or acyl,
R^3 is hydrogen or lower alkyl,
R^4 is heterocyclic(lower)alkyl,
wherein said heterocyclic group being saturated or unsaturated 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) [e.g. 2-(or 4-)-pyridylmethyl, etc.], and
R^5 is lower alkoxy or lower alkylamino.

Another preferable examples of R^1, R^2, R^3, R^4 and R^5 are as follows:

R^1 is hydrogen,
R^2 is hydrogen; acyl such as oxamoyl; lower alkanoyl; lower alkanesulfonyl; lower alkoxycarbonyl; (C_3-C_7)cycloalkanecarbonyl; di(lower)alkylamino(lower)alkanoyl; lower alkylcarbamoyl; di(lower)alkylcarbamoyl;

N-[(lower)alkylcarbamoyl(lower)alkyl]carbamoyl; C_6-C_{10} aroyl; C_6-C_{10} arenesulfonyl; C_6-C_{10} arylcarbamoyl; heterocyclic-carbonyl optionally substituted by the group consisting of acyl such as C_6-C_{10} ar(lower)alkoxycarbonyl, lower alkyl, hydroxy and oxo, said heterocyclic group being

unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s),

saturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 7- to 12-membered (more preferably 9- to 10-membered) condensed (preferably bicyclic) heterocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s), or

saturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s);

heterocyclic-carbamoyl, said heterocyclic group being

unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s),

saturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 7- to 12-membered (more preferably 9- to 10-membered) condensed (preferably bicyclic) heterocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s), or

saturated 3- to 8-membered (more preferably 5- or

6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s);

(C_6-C_{10})aryloxy(lower)alkanoyl;

heterocyclic(lower)alkanoyl, said heterocyclic group being

unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s)

saturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 7- to 12-membered (more preferably 9- to 10-membered) condensed (preferably bicyclic) heterocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s), or

saturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s);

lower alkylcarbamoyl(lower)alkanoyl;

carboxy(lower)alkanoyl; protected carboxy(lower)alkanoyl; hydroxy(lower)alkanoyl;

protected hydroxy(lower)alkanoyl;

lower alkoxy(lower)alkanoyl;

lower alkoxy(lower)alkoxycarbonyl;

amino(lower)alkoxycarbonyl;

protected amino(lower)alkoxycarbonyl;

lower alkoxycarbonyl(lower)alkylcarbamoyl;

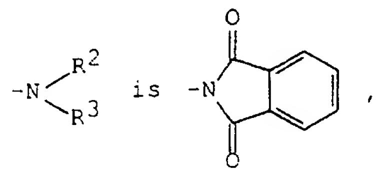
lower alkylsulfonyl(lower)alkanoyl;

hydroxy(lower)alkoxycarbonyl;

protected hydroxy(lower)alkoxycarbonyl; lower alkanoyl substituted by the group consisting of amino and hydroxy; lower alkanoyl substituted by the group consisting of protected amino and hydroxy;

amino(lower)alkanoyl; or protected amino(lower)alkanoyl;

R^3 is hydrogen or lower alkyl, or the formula:



R^4 is heterocyclic(lower)alkyl,

said heterocyclic group being

unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s),

saturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 7- to 12-membered (more preferably 9- to 10-membered) condensed (preferably bicyclic) heterocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s), or

saturated 3- to 8-membered (more preferably 5- or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s),

R^5 is lower alkoxy or lower alkylamino.

The processes for preparing the object compound (I) are explained in detail in the following.

Process 1

The object compound (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the carboxy group, or a salt thereof with the compound (III) or its reactive derivative at the amino

group, or a salt thereof.

Suitable reactive derivative at the amino group of the compound (III) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (III) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (III) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (III) with phosphorus trichloride or phosgene, and the like.

Suitable salts of the compound (III) and its reactive derivative can be referred to the acid addition salts as exemplified for the compound (I).

Suitable reactive derivative at the carboxy group of the compound (II) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester,

propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (II) to be used.

Suitable salts of the compound (II) and its reactive derivative may be the same as those for the compound (I).

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound (II) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSCD); N,N'-carbonylbis(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine, ethoxyacetylene; 1-alkoxy-1-chloroethylene, trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate;

phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; diphenylphosphorylazide; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; N-hydroxybenzotriazole (HOBT); 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine (e.g. triethylamine, etc.), pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-diiospropyl-N-ethylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 2

The object compound (I-b) or a salt thereof can be prepared by subjecting the compound (I-a) or a salt thereof to a removal reaction of the phthalimido moiety.

Suitable salts of the compound (I-a) and (I-b) can be referred to the ones as exemplified for the compound (I).

This reaction can be carried out by a conventional method which can convert the phthalimido moiety to amino moiety such as reacting with lower alkylamine (e.g. methylamine, etc.), reacting with hydrazine or its hydrate (e.g. hydrazine monohydrate, etc.), reacting with arylhydrazine or its salt (e.g. phenylhydrazine hydrochloride, etc.), reducing with a suitable reducing agent (e.g. sodium borohydride, etc.), reacting with a

combination of sodium sulfide or its hydrate (e.g. sodium sulfide monohydride, etc.) and 1,3-dicyclohexylcarbodiimide (DCC), and the like.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, alcohol (e.g. methanol, ethanol, propanol, etc.), dioxane, tetrahydrofuran, acetic acid, buffer solution (e.g. phosphate buffer, etc.), and the like, or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to heating.

Process 3

The object compound (I-c) or a salt thereof can be prepared by alkylating the amino group of a compound (I-b) or a salt thereof.

Suitable salts of the compounds (I-b) and (I-c) can be referred to the ones as exemplified for the compound (I).

Suitable alkylating agent used in this reaction may include a conventional one which is capable of alkylating amino group to alkylamino group such as dialkyl sulfate (e.g. dimethyl sulfate, diethyl sulfate, etc.), alkyl sulfonate (e.g. methyl sulfonate, etc.), alkyl halide (e.g. methyl iodide, ethyl iodide, propyl bromide, etc.), diazoalkanes (e.g. diazomethane, diazoethane, etc.), a combination of formaldehyde and a suitable reducing agent (e.g. sodium cyanoborohydride, etc.), and the like.

This reaction is preferably carried out in the presence of an inorganic or organic base such as those given in the explanation of the Process 1.

Further, this reaction is usually carried out in a

conventional solvent which does not adversely influence the reaction such as water, acetone, dichloromethane, methanol, ethanol, propanol, pyridine, N,N-dimethylformamide, or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to warming.

Process 4

The object compound (I-e) or a salt thereof can be prepared by acylating the compound (I-d) or a salt thereof.

Suitable acylating agent used in this reaction may be a conventional acylating agent which is capable of introducing the acyl group as mentioned before such as carboxylic acid, carbonic acid, sulfonic acid and their reactive derivative, for example, an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Preferable examples of such reactive derivative may include acid chloride, acid bromide, a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, alkyl carbonate (e.g. methyl carbonate, ethyl carbonate, propyl carbonate, etc.), aliphatic carboxylic acid (e.g. pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.), aromatic carboxylic acid (e.g. benzoic acid, etc.), a symmetrical acid anhydride, an activated acid amide with a heterocyclic compound containing imino function such as imidazole, 4-substituted imidazole, dimethylpyrazole, triazole and tetrazole, an activated ester (e.g. p-nitrophenyl ester, 2,4-dinitrophenyl ester,

trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyridyl ester, piperidinyl ester, 8-quinolyl thioester, or an ester with a N-hydroxy compound such as N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxybenzotriazole, 1-hydroxy-6-chlorobenzotriazole, etc.), isocyanate compound such as phenyl isocyanate, etc., and the like.

This reaction can be carried out in the presence of an organic or inorganic base such as alkali metal (e.g. lithium, sodium, potassium, etc.), alkaline earth metal (e.g. calcium, etc.), alkali metal hydride (e.g. sodium hydride, etc.), alkaline earth metal hydride (e.g. calcium hydride, etc.), alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), alkali metal alkoxide (e.g. sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.), alkali metal alkanoic acid (e.g. sodium acetate, etc.), trialkylamine (e.g. triethylamine, etc.), pyridine compound (e.g. pyridine, lutidine, picoline, 4-dimethylaminopyridine, etc.), quinoline, and the like.

In case that the acylating agent is used in a free form or its salt in this reaction, the reaction is preferably carried out in the presence of a condensing agent such as a carbodiimide compound [e.g. N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide, N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, etc.],

a ketenimine compound (e.g. N,N'-carbonylbis(2-methylimidazole), pentamethyleneketene-N-cyclohexylimine, diphenylketene-N-cyclohexylimine, etc.); an olefinic or acetylenic ether compounds (e.g. ethoxyacetylene, β-chlorovinylethyl ether), a sulfonic acid ester of N-hydroxybenzotriazole derivative [e.g. 1-(4-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole, etc.], a combination of trialkylphosphite or triphenylphosphine and carbon tetrachloride, disulfide or diazenedicarboxylate (e.g. diehyl diazenedicarboxylate, etc.), a phosphorus compound (e.g. ethyl polyphosphate, isopropyl polyphosphate, phosphoryl chloride, phosphorus trichloride, etc.), thionyl chloride, oxalyl chloride, N-ethylbenzisoxazolium salt, N-ethyl-5-phenylisoxazolium-3-sulfonate, a reagent (referred to a so-called "Vilsmeier reagent") formed by the reaction of an amide compound such as N,N-di(lower)alkylformamide (e.g. dimethylformamide, etc.), N-methylformamide or the like, with a halogen compound such as thionyl chloride, phosphoryl chloride, phosgene or the like.

The reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, acetone, dichloromethane, alcohol (e.g. methanol, ethanol, etc.), tetrahydrofuran, pyridine, N,N-dimethylformamide, etc., or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to heating.

Process 5

The object compound (I-g) or a salt thereof can be prepared by subjecting the compound (I-f) or a salt thereof to a removal reaction of the hydroxy-protective group.

Suitable salts of the compounds (I-f) and (I-g) can be referred to the ones as exemplified for the compound (I).

The present reaction is usually carried out by a conventional method such as hydrolysis, reduction, and the like.

(i) Hydrolysis :

Hydrolysis is preferably carried out in the presence of a base or an acid. Suitable base may include an alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), an alkaline earth metal hydroxide (e.g. magnesium hydroxide, calcium hydroxide, etc.), alkali metal hydride (e.g. sodium hydride, potassium hydride, etc.), alkaline earth metal hydride (e.g. calcium hydride, etc.), alkali metal alkoxide (e.g. sodium methoxide, sodium ethoxide, potassium t-butoxide, etc.), an alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), an alkaline earth metal carbonate (e.g. magnesium carbonate, calcium carbonate, etc.), an alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), and the like.

Suitable acid may include an organic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, etc.). The acidic hydrolysis using trifluoroacetic acid is usually accelerated by addition of cation trapping agent (e.g. phenol, anisole, etc.).

In case that the hydroxy-protective group is tri(lower)alkylsilyl, the hydrolysis can be carried out in the presence of tri(lower)alkylammonium fluoride (e.g. tributylammonium fluoride, etc.).

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, dichloromethane, alcohol (e.g. methanol, ethanol, etc.), tetrahydrofuran, dioxane, acetone, etc., or a mixture thereof. A liquid base or acid can be also used as the solvent.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to heating.

(ii) Reduction :

The reduction method applicable for this removal reaction may include, for example, reduction by using a combination of a metal (e.g. zinc, zinc amalgam, etc.) or a salt of chrome compound (e.g. chromous chloride, chromous acetate, etc.) and an organic or inorganic acid (e.g. acetic acid, propionic acid, hydrochloric acid, sulfuric acid, etc.); and conventional catalytic reduction in the presence of a conventional metallic catalyst such as palladium catalysts (e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, palladium hydroxide on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g. reduced nickel, nickel oxide, Raney nickel, etc.), platinum catalysts (e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), and the like.

In case that the catalytic reduction is applied, the reaction is preferably carried out in the presence of an acid (e.g. formic acid, etc.).

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, alcohol (e.g. methanol, ethanol, propanol, etc.), dioxane, tetrahydrofuran, acetic

acid, buffer solution (e.g. phosphate buffer, etc.), and the like, or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to warming.

In case that the hydroxy-protective group is allyloxycarbonyl group, it can be deprotected by hydrogenolysis using a palladium compound.

Suitable palladium compound used in this reaction may be palladium on carbon, palladium hydroxide on carbon, palladium chloride, a palladium-ligand complex such as tetrakis(triphenylphosphine)palladium(0), bis(dibenzylideneacetone)palladium(0), di[1,2-bis(diphenyl phosphino)ethane]palladium(0), tetrakis(triphenylphosphite)palladium(0), tetrakis(triethyl phosphite)palladium(0), and the like.

This reaction can preferable be carried out in the presence of a scavenger of allyl group generated in situ, such as amine (e.g. morpholine, N-methylaniline, etc.), an activated methylene compound (e.g. dimedone, benzoylacetate, 2-methyl-3-oxovaleric acid, etc.), a cyanohydrin compound (e.g. α-tetrahydropyranyloxybenzyl-cyanide, etc.), lower alkanoic acid or a salt thereof (e.g. formic acid, acetic acid, ammonium formate, sodium acetate, etc.), N-hydroxysuccinimide, and the like.

This reaction can be carried out in the presence of a base such as lower alkylamine (e.g. butylamine, triethylamine, etc.), pyridine, and the like.

When palladium-ligand complex is used in this reaction, the reaction can preferably be carried out in the presence of the corresponding ligand (e.g. triphenylphosphine, triphenyl phosphite, triethyl phosphite, etc.).

This reaction is usually carried out in a conventional solvent which does not adversely influence

the reaction such as water, methanol, ethanol, propanol, dioxane, tetrahydrofuran, acetonitrile, chloroform, dichloromethane, dichloroethane, ethyl acetate, etc., or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to warming.

The reaction can be selected according to the kind of hydroxy-protective group to be eliminated.

Process 6

The compound (I-i) or a salt thereof can be prepared by reacting the compound (I-h) or a salt thereof with the compound (IV) or its reactive derivative at the amino group, or a salt thereof.

Suitable salts of the compounds (I-g) and (I-h) may be the same as those for the compound (I).

Suitable salts of the compound (IV) may be the same acid addition salts as exemplified for the compound (I).

Suitable reactive derivative of the compound (IV) can be referred to the ones as exemplified for the compound (III).

The reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, acetone, dioxane, dimethylformamide, dichloromethane, chloroform, pyridine, etc., or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to warming.

Process 7

The compound (I-k) or a salt thereof can be prepared by subjecting the compound (I-j) or a salt thereof to a removal reaction of the carboxy-protective group on R_b^2.

Suitable salts of the compounds (I-k) and (I-j) may be the same as those for the compound (I).

The reaction is usually carried out in substantially the same manner as those for the process 5, and therefore the reagents to be used and the reaction condition (e.g. solvent, reaction temperature, etc.) can be referred to those of the Process 5.

Process 8

The compound (I-m) or a salt thereof can be prepared by subjecting the compound (I-ℓ) or a salt thereof to a removal reaction of the amino-protective group on R^2_d.

Suitable salts of the compounds (I-ℓ) and (I-m) may be the same as those for the compound (I).

The reaction is usually carried out in substantially the same manner as those for the Process 5, and therefore the reagents to be used and the reaction condition (e.g. solvent, reaction temperature, etc.) can be referred to those of the Process 5.

Process 9

The compound (I-o) or a salt thereof can be prepared by subjecting the compound (I-n) or a salt thereof to a removal reaction of the hydroxy-protective group on R^2_f.

Suitable salts of the compounds (I-n) and (I-o) may be the same as those for the compound (I).

The reaction is usually carried out in substantially the same manner as those for the Process 5, and therefore the reagents to be used and the reaction condition (e.g. solvent, reaction temperature, etc.) can be referred to those of the Process 5.

Process 10

The compound (I-q) or a salt thereof can be prepared by reacting the compound (I-p) or a salt thereof with lower alkylamine.

Suitable salts of the compounds (I-p) and (I-q) may be the same as those for the compound (I).

The reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, acetone, dichloromethane, alcohol (e.g. methanol, ethanol, etc.), tetrahydrofuran, pyridine, N,N-dimethylformamide, etc., or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to warming.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

The object compound (I) can be transformed into its salt in a conventional manner.

It is to be noted that the compound (I) and the other compounds may include one or more stereoisomers due to asymmetric carbon atoms, and all of such isomers and mixture thereof are included within the scope of this invention.

Collagenases initiate the degradation of collagen in vertebrates and in addition to their normal function in the metabolism of connective tissue and wound healing, it has been implicated in a number of pathological conditions such as joint destruction in rheumatoid arthritis, periodontal disease, corneal ulceration, tumor metastasis,

osteoarthritis, decubitus restenosis after the percutaneous transluminal coronary angiopsty, osteoporosis, proriasis, chronic active heatitis, autoimmune keratitis, and the like, and therefore the compound of the present invention is useful for treating and/or preventing such pathological conditions.

For therapeutic purpose, the peptide compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, solution, suspension, emulsion, sublingual tablet, suppositories, ointment, and the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound (I) will vary depending upon the age and condition of the patient, in the case of intravenous administration, a daily dose of 0.01 - 100 mg of the active ingredient per kg weight of a human being, in the case of intramuscular administration, a daily dose of 0.05 - 100 mg of the same per kg weight of a human being, in case of oral administration, a daily dose of 0.1 - 100 mg of the same per kg weight of a human being is generally given for the treatment of collagenase-mediated diseases.

In order to illustrate the usefulness of the object compound (I), the pharmacological test data of a

representative compound of the compound (I) are shown in the following.

Inhibitory activity of collagenase

1. Test method

Human collagenase was prepared from the culture medium of human skin fibroblast stimulated by interleukin-1β (1 ng/ml). Latent collagenase was activated by incubation with trypsin (200 μg/ml) at 37°C for 60 minutes and the reaction was stopped by adding soybean trypsin inhibitor (800 μg/ml). Collagenase activity was determined using FTTC-labeled calf skin type I collagen. FITC-collagen (2.5 mg/ml) was incubated at 37°C for 120 minutes with the activated collagenase and test compound in 50 mM Tris buffer (containing 5 mM $CaCl_2$, 200 mM NaCl and 0.02% NaN_3, pH 7.5). After stopping the enzyme reaction by adding equal volume of 70% ethanol-200 mM Tris buffer (pH 9.5), the reaction mixture was centrifuged, and collagenase activity was estimated by measuring the fluorescence intensity of supernatant at 495 nm (excitation) and 520 nm (emission).

2. Test Compound

Compound A (The compound of Example 12-4)

3. Test Result

Inhibitory activity

Test Compound	IC_{50} (nM)
Compound A	1.5

The following examples are given for purpose of illustrating the present invention in detail.

In these examples, there are employed the following abbreviations in addition to the abbreviations adopted by the IUPAC-IUB.

DEF	:	dimethylformamide
DMSO	:	dimethyl sulfoxide
HOBT	:	N-hydroxybenzotriazole
WSCD	:	1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

Thionyl chloride (73 ml) was added dropwise into absolute ethanol (300 ml) at 0°C. After L-4-pyridylalanine D-tartrate (31.6 g) was added portionwise, the suspension was slowly heated to reflux and stirred overnight. The solvent was evaporated to one third volume in vacuo, and was triturated with ethyl acetate to give L-4-pyridylalanine ethyl ester dihydrochloride (24.7 g).

$[\alpha]_D^{25}$ = +24.0° (c 0.99, H_2O)

mp : 185-186°C

NMR (D_2O, δ) : 3.60 (1H, dd, J=14, 7Hz), 3.68 (1H, dd, J=14, 8Hz), 3.82 (3H, s), 4.71 (1H, dd, J=8, 7Hz), 8.08 (2H, d, J=7Hz), 8.80 (2H, d, J=7Hz)

HPLC : 8.4 minutes(min.) (Crownpak CR(+), 4 mmφ x 15 cm, pH 1.0 $HClO_4$aq., 210 nm, flow rate 0.5 ml/min., at R.T.)

MASS : M+H=181

Preparation 2

To a solution of (3R)-3-carboxy-5-methyl-2-(phthalimidomethyl)hexanoic acid tert-butyl ester (5.00 g) in DMF (50 ml) were added HOBT (2.08 g), WSCD (2.39 g), L-4-pyridylalanine methyl ester dihydrochloride (3.90 g), and N,N-diisopropyl-N-ethylamine (4.03 g) at 0°C. The mixture was stirred at room temperature for 15 hours. The reaction mixture was poured into brine, and was extracted with ethyl acetate. The extract was washed with saturated ammonium chloride, saturated sodium bicarbonate, and brine successibly. The organic layer was dried over magnesium sulfate ($MgSO_4$) and was concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent : ethyl acetate) to give N-[(2R)-4-tert-butoxy-2-isobutyl-3-(phthalimidomethyl)succinyl]-L-4-pyridylalanine methyl ester (5.63 g).

mp : 66-69°C

NMR ($CDCl_3$, δ) : 0.74 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz), 1.11 (1H, ddd, J=13, 9, 4Hz), 1.27 (9H, s), 1.50 (1H, m), 1.71 (1H, ddd, J=13, 9, 4Hz), 2.65 (1H, m), 2.92 (1H, m), 3.11 (1H, dd, J=14, 8Hz), 3.28 (1H, dd, J=14, 6Hz), 3.58-3.64 (2H, m), 3.75 (3H, s), 5.00 (1H, ddd, J=8, 7.5, 6Hz), 6.88 (1H, d, J=7.5Hz), 7.18 (2H, d, J=7Hz), 7.69-7.77 (2H, m), 7.81-7.90 (2H, m), 8.49 (2H, d, J=7Hz)

HPLC : 9.3, 9.9 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 35:65, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=552

Preparation 3

To a solution of N-[(2R)-4-tert-butoxycarbonyl-2-isobutyl-3-(phthalimidomethyl)succinyl]-L-4-pyridylalanine methyl ester (5.52 g) in dichloromethane (30 ml) was added trifluoroacetic acid (30 ml) at 0°C. The reaction mixture was stirred at room temperature for 1.5 hours. After the solvent was concentrated in vacuo, the residue was triturated with ethyl acetate to give N-[(2R,3R)-4-hydroxy-2-isobutyl-3-(phthalimidomethyl)succinyl)-L-4-pyridylalanine methyl ester trifluoroacetate (3.50 g).

$[\alpha]_D^{25}$ = -14.7° (c 0.30, 1N-HClaq.)

mp : 190-194°C

NMR (DMSO-d_6, δ) : 0.78 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.90 (1H, ddd, J=13, 11, 2Hz), 1.36 (1H, m), 1.51 (1H, ddd, J=13, 11, 2Hz), 2.43-2.57 (1H, m), 2.62-2.76 (2H, m), 3.10 (1H, dd, J=14, 12Hz), 3.40 (1H, dd, J=14, 5Hz), 3.50 (1H, m), 3.65 (3H, s), 4.89 (1H, ddd, J=12, 8, 5Hz), 7.75 (2H, d, J=6Hz), 7.82-7.92 (4H, m), 8.62 (2H, d, J=6Hz), 8.72 (1H, d, J=8Hz)

HPLC : 3.9 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0

ml/min., at R.T.)

MASS : M+H=496

Preparation 4

Thionyl chloride (73 ml) was added dropwise into absolute ethanol (300 ml) at 0°C. After L-4-pyridylalanine D-tartrate (31.6 g) was added portionwise, the suspension was slowly heated to reflux and stirred overnight. The solvent was evaporated to one third volume in vacuo, and was triturated with ethyl acetate to give L-4-pyridylalanine ethyl ester dihydrochloride (24.7 g).

$[\alpha]_D^{24}$ = +22.6° (c 0.54, 1N-HClaq.)

mp : 160-166°C

NMR (DMSO-d_6, δ) : 1.14 (3H, t, J=7Hz), 3.47 (1H, dd, J=15, 7.5Hz), 3.55 (1H, dd, J=15, 7Hz), 4.15 (2H, m), 4.55 (1H, br), 8.10 (2H, d, J=7Hz), 8.91 (2H, d, J=7Hz), 8.98 (1H, br)

HPLC : 12.3 min. (Crownpak CR(+), 4 mmϕ x 15 cm, pH 1.0 $HClO_4$aq., 210 nm, flow rate 0.6 ml/min., at R.T.)

MASS : M+H=195

Preparation 5

L-4-Pyridylalanine ethyl ester dihydrochloride (24.3 g) was dissolved in H_2O and the pH was adjusted to 8-9 by the addition of sodium hydrogen carbonate. The solution was saturated with sodium chloride and was extracted with chloroform. The extract was dried over $MgSO_4$ and concentrated to dryness to give L-4-pyridylalanine ethyl ester as a pale yellow oil (15.6 g).

NMR ($CDCl_3$, δ) : 1.23 (3H, t, J=7Hz), 1.49 (2H, br), 2.86 (1H, dd, J=14, 7.5Hz), 3.05 (1H, dd, J=14, 6Hz), 3.73 (1H, dd, J=7.5, 6Hz), 4.17 (2H, q, J=7Hz), 7.15 (2H, d, J=7Hz), 8.53 (2H, d, J=7Hz)

HPLC : 11.2 min. (Crownpak CR(+), 4 mmϕ x 15 cm, pH 1.0 $HClO_4$aq., 210 nm, flow rate 0.6 ml/min., at R.T.)

MASS : M+H=195

Preparation 6

L-4-Pyridylalanine ethyl ester (14.79 g) was dissolved into a solution of 20% methylamine in methanol (60 ml), and the mixture was stirred for 4 hours at room temperature. The solution was evaporated to give L-4-pyridylalanine methylamide (12.59 g).

$[\alpha]_D^{24}$ = +20.7° (c 0.55, MeOH)

mp : 48-52°C

NMR (DMSO-d_6, δ) : 1.71 (2H, br), 2.57 (3H, d, J=5Hz), 2.62 (1H, dd, J=14, 8Hz), 2.90 (1H, dd, J=14, 5Hz), 3.38 (1H, dd, J=8, 5Hz), 7.21 (2H, d, J=6Hz), 7.82 (1H, q, J=5Hz), 8.44 (2H, d, J=6Hz)

HPLC : 11.2 min. (Crownpak CR(+), 4 mmϕ x 15 cm, pH 1.0 $HClO_4$aq., 210 nm, flow rate 0.6 ml/min., at R.T.)

MASS : M+H=180

Preparation 7

To a solution of (3R)-3-carboxy-5-methyl-2-(phthalimidomethyl)hexanoic acid tert-butyl ester (10.13 g) in DMF (100 ml) were added HOBT (3.87 g), WSCD·HCl (5.49 g), and L-4-pyridylalanine methylamine (4.89 g) at 0°C. The mixture was stirred at room temperature for 3 hours. The reaction mixture was poured into brine, and was extracted with ethyl acetate. The extract was washed with saturated ammonium chloride, saturated sodium bicarbonate, and brine successibly. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent : methanol/ethyl acetate = 1/10) to give N-[(2R)-4-tert-butoxy-2-isobutyl-3-(phthalimidomethyl)succinyl]-L-4-pyridylalanine methylamide (13.8 g).

mp : 92-95°C

NMR ($CDCl_3$, δ) : 0.67-0.88 (7H, m), 1.13 (1H, m), 1.28

(9Hx3/4, s), 1.31 (9Hx1/4, s), 1.65 (1H, m), 2.50 (1Hx1/4, m), 2.62 (1Hx3/4, m), 2.77 (3Hx3/4, d, J=5Hz), 2.80 (3Hx1/4, d, J=5Hz), 2.90 (1H, m), 3.11 (1H, m), 3.27 (1H, m), 3.52-3.60 (2H, m), 4.72 (1Hx1/4, m), 4.78 (1Hx3/4, m), 6.31 (1Hx3/4, m), 6.48 (1Hx1/4, m), 6.94 (1Hx3/4, d, J=8Hz), 7.14 (1Hx1/4, d, J=8Hz), 7.20 (2H, d, J=7Hz), 7.68-7.78 (2H, m), 7.80 (2H, m), 8.47 (2Hx3/4, d, J=7Hz), 8.50 (2Hx1/4, d, J=7Hz)

HPLC : 6.0, 6.6 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 35:65, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=551

Preparation 8

N-[(2R)-4-Hydroxy-2-isobutyl-3-(phthalimidomethyl)-succinyl]-L-4-pyridylalanine methylamide trifluoroacetate was obtained in substantially the same manner as that of Preparation 3.

mp : 180-185°C

NMR (DMSO-d_6, δ) : 0.72-0.87 (6H, m), 0.92 (1H, m), 1.33 (1H, m), 1.49 (1H, m), 2.47-2.70 (3H, m), 2.59 (3Hx1/4, d, J=5Hz), 2.62 (3Hx3/4, d, J=5Hz), 2.97 (1H, dd, J=14, 11.5Hz), 3.17 (1H, dd, J=14, 5Hz), 3.48 (1H, m), 4.59 (1Hx1/4, m), 4.75 (1Hx3/4, m), 7.68 (2Hx3/4, d, J=7Hz), 7.72 (2Hx1/4H, d, J=7Hz), 7.80-7.91 (4H, m), 7.96 (1H, m), 8.40 (1Hx1/4, d, J=8Hz), 8.54 (1Hx3/4, d, J=8Hz), 8.57 (2Hx3/4, d, J=8Hz), 8.72 (2Hx1/4, d, J=7Hz)

HPLC : 5.1, 8.3 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., ar R.T.)

MASS : M+H=495

Preparation 9

L-2-Pyridylalanine methyl ester dihydrochloride was obtained in substantially the same manner as that of Preparation 4.

$[\alpha]_D^{22}$ = +28.3° (c 1.03, H_2O)

mp : 209-213°C

NMR (DMSO-d_6, δ) : 3.58 (2H, d, J=7Hz), 3.67 (3H, s), 4.62 (1H, br), 7.70 (1H, m), 7.80 (1H, br d, J=7.5Hz), 8.23 (1H, m), 8.71 (1H, d, J=5Hz), 8.91 (2H, br)

HPLC : 10.4 min. (Crownpak CR(+), 4 mmϕ x 15 cm, pH 1.0 $HClO_4$aq., 210 nm, flow rate 0.5 ml/min., at R.T.)

MASS : M+H=181

Preparation 10

L-2-Pyridylalanine methyl ester dihydrochloride (10.0 g) was dissolved in saturated sodium hydrogen carbonate (10 ml). The solution was saturated with sodium chloride and extracted with chloroform (300 ml x 3). After the extract was concentrated to dryness, the residue was dissolved in 40% methylamine in methanol (30 ml). The mixture was stirred for 1 hour at room temperature. The solution was evaporated to give L-2-pyridylalanine methylamide (7.0 g).

Rf : 0.19 (methanol/chloroform = 1/5)

Preparation 11

N-[(2R,3R)-4-tert-Butoxy-2-isobutyl-3-(phthalimidomethyl)succinyl]-L-2-pyridylalanine methyl ester was obtained in substantially the same manner as that of Preparation 7.

Rf : major isomer 0.42, minor isomer 0.46 (methanol/chloroform = 1/10)

Preparation 12

N-[(2R)-4-tert-Butoxy-2-isobutyl-3-(phthalimidomethyl)-succinyl]-L-2-pyridylalanine methylamide (14.0 g) was

dissolved in trifluoroacetic acid (30 ml) at 0°C. The reaction mixture was stirred at room temperature for 0.5 hour. After the solvent was concentrated in vacuo, the residue was poured into saturated sodium hydrogen carbonate. The solution was extracted with chloroform. The organic layer was concentrated in vacuo and the residue was triturated with ethyl acetate to give N-[(2R)-4-hydroxy-2-isobutyl-3-(phthalimidomethyl)succinyl)-L-2-pyridylalanine methylamide (3.50 g).

HPLC : 3.7, 4.8 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

Preparation 13

To a stirred suspension of glycine methyl ester hydrochloride (1.70 g) in dichloromethane (15 ml) was added triethylamine (3.01 g) and phenyl chloroformate (2.12 g) at 0°C. The mixture was stirred at 0°C for 30 minutes. The reaction mixture was poured into water and was extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by a silica gel column chromatography (ethyl acetate:hexane = 1:1) to give N-phenoxycarbonylglycine methyl ester (1.37 g) as a white crystal.

mp : 46-47°C

NMR ($CDCl_3$, δ) : 3.79 (3H, s), 4.07 (2H, d, J=7Hz), 5.52 (1H, br), 7.13 (2x1H, d, J=7.5Hz), 7.20 (1H, dd, J=7.5, 7.5Hz), 7.36 (2x1H, dd, J=7.5, 7.5Hz)

MASS : M+H=210

Preparation 14

N-[(2R)-4-tert-Butoxy-2-isobutyl-3-phthalimidomethylsuccinyl]-L-3-pyridylalanine methyl ester was obtained in substantially the same manner as that of

Preparation 7.

mp : 65-68°C

NMR ($CDCl_3$, δ) : 0.75-0.90 (6H, m), 1.10 (1H, ddd, J=11, 11, 3Hz), 1.27 (3x3H, s), 1.50 (1H, m), 1.70 (1H, m), 2.67 (1H, m), 2.90 (1H, m), 3.13 (1H, dd, J=14, 8Hz), 3.27 (1H, dd, J=14, 6Hz), 3.52 (1H, dd, J=14, 7Hz), 3.69 (1H, dd, J=14, 5Hz), 3.74 (3H, s), 4.98 (1H, m), 6.96 (1H, dd, J=14, 5Hz), 7.22 (1H, dd, J=7.5, 5Hz), 7.62 (1H, m), 7.68-7.76 (2H, m), 7.80 (2H, m), 8.40-8.52 (2H, m)

HPLC : 12.4 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, acetonitrile:water:trifluoroacetic acid (MeCN:H_2O:TFA) = 35:65:0.05, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=552

Preparation 15

N-[(2R,3R)-4-Hydroxy-2-isobutyl-3-phthalimidomethylsuccinyl]-L-3-pyridylalanine methyl ester trifluoroacetate was obtained in substantially the same manner as that of Preparation 8.

$[\alpha]_D^{25}$ = -18.5° (c 0.17, 1N-HClaq.)

mp : 174-177°C (dec.)

NMR (DMSO-d_6, δ) : 0.77 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.90 (1H, m), 1.35 (1H, m), 1.50 (1H, m), 2.45-2.58 (1H, m), 2.68 (1H, m), 2.79 (1H, dd, J=13, 5Hz), 3.05 (1H, dd, J=13, 11Hz), 3.32 (1H, dd, J=13, 4Hz), 3.54 (1H, dd, J=13, 12Hz), 3.64 (3H, s), 4.79 (1H, ddd, J=11, 8, 4Hz), 7.69 (1H, dd, J=7.5, 6Hz), 7.81-7.91 (4H, m), 8.23 (1H, d, J=7.5Hz), 8.51 (1H, d, J=6Hz), 8.69 (1H, d, J=8Hz), 8.73 (1H, s)

HPLC : 4.1 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN : 0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=496

Example 1-1)

To a solution of N-[(2R,3R)-4-hydroxy-2-isobutyl-3-(phthalimidomethyl)succinyl]-L-4-pyridylalanine methyl ester trifluoroacetate (3.26 g) and HOBT (0.87 g) in DMF (30 ml) was added WSCD (1.00 g) at 0°C. After the mixture was stirred for 10 minutes, O-benzylhydroxylamine hydrochloride (1.02 g) and N,N-diisopropyl-N-ethylamine (0.84 g) were added. The mixture was stirred at room temperature for 15 hours. The mixture was poured into brine (100 ml). The precipitate was collected by filtration and was washed with water and ethyl acetate to give N-[(2R,3R)-4-(N-benzyloxyamino)-2-isobutyl-3-(phthalimidomethyl)succinyl]-L-4-pyridylalanine methyl ester (2.10 g).

$[\alpha]_D^{25}$ = -52.8° (c 0.30, DMSO)

mp : 245-248°C (dec.)

NMR ($DMSO-d_6$, δ) : 0.70-0.84 (1H, m), 0.76 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 1.30-1.47 (2H, m), 2.29-2.57 (3H, m), 2.89 (1H, dd, J=14, 12Hz), 3.20 (1H, dd, J=14, 4Hz), 3.45 (1H, m), 3.64 (3H, s), 4.25 (1H, d, J=12Hz), 4.54 (1H, d, J=12Hz), 4.77 (1H, ddd, J=12, 8, 4Hz), 7.05 (2H, d, J=7.5Hz), 7.15-7.27 (3H, m), 7.30 (2H, d, J=7Hz), 7.85 (4H, s), 8.28 (2H, d, J=7Hz), 8.64 (1H, d, J=8Hz), 11.06 (1H, s)

HPLC : 9.6 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=601

Example 1-2)

To a solution of N-[(2R)-4-hydroxy-2-isobutyl-3-(phthalimidomethyl)succinyl]-L-4-pyridylalanine methylamide trifluoroacetate (5.18 g) and HOBT (1.27 g) in DMF (50 ml)

was added WSCD (1.46 g) at 0°C. After the mixture was stirred for 10 minutes, O-benzylhydroxylamine hydrochloride (1.63 g) and N,N-diisopropyl-N-ethylamine (1.34 g) were added. The mixture was stirred at room temperature for 4 hours. The mixture was poured into brine (100 ml). The precipitate was collected by filtration and was washed with water and ethyl acetate to give N-[(2R,3R)-4-(N-benzyloxyamino)-2-isobutyl-3-(phthalimidomethyl)succinyl]-L-4-pyridylalanine methylamide (3.40 g).

$[\alpha]_D^{25}$ = +2.8° (c 0.10, DMSO)

mp : 263-269°C (dec.)

NMR (DMSO-d_6, δ) : 0.70-0.85 (1H, m), 0.73 (3H, d, J=7Hz), 0.81 (3H, d, J=7Hz), 1.22-1.45 (2H, m), 2.21 (1H, ddd, J=13, 3, 2Hz), 2.32 (1H, ddd, J=11, 11, 3Hz), 2.50 (1H, dd, J=13, 11Hz), 2.61 (3H, d, J=5Hz), 2.80 (1H, dd, J=14, 11Hz), 3.00 (1H, dd, J=14, 5Hz), 3.40 (1H, dd, J=13, 11Hz), 4.26 (1H, d, J=12Hz), 4.55 (1H, d, J=12Hz), 4.67 (1H, ddd, J=11, 8, 5Hz), 7.03-7.09 (2H, m), 7.15-7.25 (3H, m), 7.30 (2H, d, J=6Hz), 7.85 (4H, s), 7.90 (1H, d, J=5Hz), 8.23 (2x1H, d, J=6Hz), 8.45 (1H, d, J=8Hz)

HPLC : 6.2 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=600

Example 1-3)

To a solution of N-[(2R)-4-hydroxy-2-isobutyl-3-(phthalimidomethyl)succinyl]-L-2-pyridylalanine methylamide (7.0 g) and HOBT (2.9 g) in DMF (140 ml) was added WSCD (3.3 g) at room temperature. After the mixture was stirred for 10 minutes, O-benzylhydroxylamine hydrochloride (3.4 g) and N,N-diisopropyl-N-ethylamine (5 ml) were added. The mixture was stirred at room temperature for 5 hours. The mixture was poured into ethyl acetate (100 ml). The insoluble solid was

collected by filtration to give N-[(2R)-4-(N-benzyloxyamino)-2-isobutyl-3-(phthalimidomethyl)succinyl]-L-2-pyridylalanine methylamine (3.50 g).

HPCL : 9.3 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

Example 2-1)

N-[(2R,3R)-4-(N-Benzyloxyamino)-2-isobutyl-3-(phthalimidomethyl)succinyl]-L-4-pyridylalanine methyl ester (2.51 g) was dissolved into a solution of 40% methylamine in methanol (50 ml), and the mixture was stirred for 15 hours at room temperature. The solution was evaporated and the residue was dissolved into 1N-hydrochloric acid. The solution was evaporated again and the residue was triturated with water. The precipitate was filtered off and the filtrate was evaporated. The residue was triturated with methanol - ethyl acetate to give N-[(2R,3R)-3-aminomethyl-4-(N-benzyloxyamino)-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide dihydrochloride (2.22 g).

$[\alpha]_D^{25}$ = -33.0° (c 0.32, 1N-HClaq.)

mp : 192-199°C

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.84 (1H, m), 1.25 (1H, m), 1.40 (1H, m), 2.30-2.46 (2H, m),2.52-2.80 (2H, m), 2.60 (3H, d, J=4.5Hz), 3.14 (1H, dd, J=14, 11Hz), 3.28 (1H, dd, J=14, 5Hz), 4.67 (1H, ddd, J=11, 8, 5Hz), 4.83 (1H, d, J=11Hz), 4.87 (1H, d, J=11Hz), 7.31-7.48 (5H, m), 8.00 (2H, d, J=7Hz), 8.11 (2H, br), 8.21 (1H, q, J=4.5Hz), 8.63 (1H, d, J=8Hz), 8.91 (2H, d, J=7Hz)

MASS : M+H=470

Example 2-2)

To a suspension of N-[(2R,3R)-4-(N-benzyloxyamino)-2-

isobutyl-3-(phthalimidomethyl)succinyl]-4-pyridylalanine methylamide (484 mg) in ethanol was added hydrazine monohydrate (0.5 ml). The mixture was refluxed for 2 hours. The solution was evaporated and to the residue was added chloroform. After the insoluble material was filtered off, the filtrate was concentrated in vacuo to give N-[(2R,3R)-3-aminomethyl-4-(N-benzyloxyamino)-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide (293 mg).

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.74-0.89 (1H, m), 0.79 (3H, d, J=7Hz), 1.18-1.38 (2H, m), 1.87-2.00 (2H, m), 2.25 (1H, m), 2.41 (1H, m), 2.57 (3H, d, J=4.5Hz), 2.80 (1H, dd, J=13, 10Hz), 2.94 (1H, dd, J=13, 4Hz), 4.55 (1H, ddd, J=10, 8, 4Hz), 4.78 (2H, s), 7.18-7.43 (7H, m), 7.87 (1H, d, J=4.5Hz), 8.30 (1H, d, J=8Hz), 8.45 (2H, d, J=7Hz)

MASS : M+H=470

Example 2-3)

To a suspension of N-(2R,3R)-4-(N-benzyloxyamino)-2-isobutyl-3-(phthalimidomethyl)succinyl]-L-2-pyridylalanine methylamide (3.5 g) in ethanol was added hydrazine monohydrate (3.5 ml). The mixture was refluxed for 30 minutes. The solution was evaporated and to the residue was added chloroform. After the insoluble material was filtered off, the filtrate was evaporated and triturated with ethyl acetate to give N-[(2R,3R)-3-aminomethyl-4-(N-benzyloxyamino)-2-isobutylsuccinyl]-L-2-pyridylalanine methylamide (1.7 g).

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.73-0.86 (1H, m), 0.77 (3H, d, J=7Hz), 1.15-1.40 (2H, m), 1.84-1.98 (2H, m), 2.19 (1H, dd, J=13, 10Hz), 2.38 (1H, m), 2.55 (3H, d, J=4Hz), 2.95 (1H, dd, J=14, 11Hz), 3.07 (1H, dd, J=14, 5Hz), 4.71 (1H, ddd, J=11, 8, 5Hz), 4.77 (2H, s), 7.20 (1H, dd, J=7.5, 5Hz), 7.26 (1H, d, J=7.5Hz), 7.31-7.42 (5H, m), 7.64-7.76 (2H,

m), 8.25 (1H, d, J=7.5Hz), 8.46 (1H, br d, J=5Hz)
MASS : M+H=470

Example 3

To a solution of N-[(2R,3R)-3-aminomethyl-4-(N-benzyloxyamino)-2-isobutylsuccinyl]-L-2-pyridylalanine methylamide (50 mg) in methanol (10 ml) was added 37% formaldehyde solution (87 mg). After being stirred for 30 minutes sodium cyanoborohydride (67 mg) was added and the pH was adjusted to 3 by the addition of 1N hydrochloric acid (HCl). The mixture was stirred at room temperature for 30 minutes. Methanol was evaporated and the residue was poured into chloroform and the solution was extracted with 1N-HCl. The aqueous layer was neutralized with sodium hydrogen carbonate and re-extracted with chloroform. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was triturated with ethyl acetate to give N-[(2R,3R)-4-(N-benzyloxyamino)-2-isobutyl-3-(methylaminomethyl)-succinyl]-L-2-pyridylalanine methylamide (412 mg).

$[\alpha]_D^{23}$ = -39.2° (c 0.13, 1N-HClaq.)
mp : 179-182°C
NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=6Hz), 0.77 (3H, d, J=6Hz), 0.80 (1H, m), 1.19-1.40 (2H, m), 1.86 (0.5x1H, s, rotamer), 2.13 (0.5x1H, s, rotamer), 1.92-2.52 (4H, m), 2.57 (3H, d, J=5Hz), 2.93-3.13 (2H, m), 4.67-4.85 (3H, m), 7.17-8.40 (12H, m)
TLC : Rf 0.20 ($CHCl_3$:MeOH=5:1)

Example 4-1)

To a solution of N-[(2R,3R)-N-3-aminomethyl-4-(N-benzyloxyamino-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide (247 mg) and picolinic acid (62 mg) in DMF (5 ml) were added HOBT (75 mg) and WSCD (90 mg) at 0°C. The mixture was stirred at 0°C for 1.5 hours. DMF was evaporated and the residue was poured into water. The precipitate was collected

by filtration and washed with water and ethyl acetate to give N-[(2R,3R)-4-(N-benzyloxyamino)-2-isobutyl-3-[(2-pyridylcarbonyl)aminomethyl]succinyl]-L-4-pyridylalanine methylamide (136 mg).

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=7Hz), 0.79 (3H, d, J=7Hz), 0.84 (1H, m), 1.29 (1H, m), 1.37 (1H, m), 2.36 (1H, ddd, J=10, 9, 4Hz), 2.45-2.63 (1H, m), 2.57 (3H, d, J=4.5Hz), 2.78-2.91 (2H, m), 2.97 (1H, dd, J=14, 6Hz), 3.18 (1H, m), 4.57 (1H, m), 4.57 (1H, d, J=11Hz), 4.71 (1H, d, J=11Hz), 7.20-7.33 (7H, m), 7.60 (1H, m), 7.87 (1H, q, J=4.5Hz), 7.95-8.05 (2H, m), 8.25 (1H, dd, J=6, 6Hz), 8.37 (2H, d, J=7Hz), 8.45 (1H, d, J=8Hz), 8.62 (1H, br d, J=5Hz), 11.10 (1H, s)

HPLC : 10.1 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=575

The following compounds were obtained in substantially the same manner as that of Example 4-1).

Example 4-2)

N-[(2R,3R)-4-(N-Benzyloxyamino)-2-isobutyl-3-[(6-methylpyridin-2-yl)carbonylaminomethyl]succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{25}$ = -23.5° (c 0.21, 1N-HClaq.)

mp : 248-254°C

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.84 (1H, m), 1.30 (1H, m), 1.39 (1H, m), 2.35 (1H, ddd, J=10, 9, 4Hz), 2.45-2.63 (1H, m), 2.48 (3H, s), 2.58 (3H, d, J=5Hz), 2.80-2.91 (1H, m), 2.85 (1H, dd, J=14, 11Hz), 2.97 (1H, dd, J=14, 5Hz), 3.13 (1H, m), 4.55 (1H, d, J=11Hz), 4.58 (1H, ddd, J=11, 8, 5Hz), 4.75 (1H, d, J=11Hz), 7.20-7.33

(7H, m), 7.45 (1H, br d, J=7.5Hz), 7.78-7.92 (3H, m), 8.14 (1H, dd, J=6, 6Hz), 8.38 (2H, d, J=6Hz), 8.43 (1H, d, J=8Hz), 11.13 (1H, s)

HPLC : 6.3 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=589

Example 4-3)

N-[(2R,3R)-4-(N-Benzyloxyamino)-2-isobutyl-3-[(2-pyridylcarbonyl)aminomethyl]succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{25}$ = -21.6° (c 0.27, 1N-HClaq.)

mp : 252-256°C (dec.)

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.84 (1H, m), 1.30 (1H, m), 1.37 (1H, m), 2.36 (1H, ddd, J=9, 9, 4Hz), 2.47-2.61 (1H, m), 2.57 (3H, d, J=4.5Hz), 2.78-2.91 (2H, m), 2.91 (1H, dd, J=14, 5Hz), 3.20 (1H, m), 4.57 (1H, m), 4.57 (1H, d, J=11Hz), 4.72 (1H, d, J=11Hz), 7.20-7.31 (7H, m), 7.60 (1H, m), 7.87 (1H, q, J=4.5Hz), 7.96-8.05 (2H, m), 8.26 (1H, dd, J=6, 6Hz), 8.37 (2H, d, J=7Hz), 8.45 (1H, d, J=8Hz), 8.63 (1H, br d, J=4Hz), 11.09 (1H, s)

HPLC : 10.4 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=575

Example 4-4)

N-[(2R,3R)-4-(N-Benzyloxyamino)-2-isobutyl-3-[(3-pyridylcarbonyl)aminomethyl]succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{25}$ = -23.8° (c 0.20, 1N-HClaq.)

mp : 246-250°C (dec.)

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=7Hz), 0.77-0.90 (1H, m), 0.80 (3H, d, J=7Hz), 1.28 (1H, m), 1.40 (1H, m), 2.33 (1H, ddd, J=9, 9, 4Hz), 2.45-2.56 (1H, m), 2.59 (3H, d, J=4.5Hz), 2.74-3.03 (2H, m), 2.85 (1H, dd, J=14, 11Hz), 2.98 (1H, dd, J=14, 5Hz), 4.58 (1H, d, J=12Hz), 4.61 (1H, m), 4.74 (1H, d, J=12Hz), 7.21-7.32 (7H, m), 7.49 (1H, dd, J=7.5, 5Hz), 7.88 (1H, q, J=4.5Hz), 8.12 (1H, br d, J=7.5Hz), 8.33-8.45 (2H, m), 8.38 (2H, d, J=6Hz), 8.68 (1H, d, J=5Hz), 8.95 (1H, s), 11.04 (1H, s)

HPLC : 9.6 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 20:80, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=575

Example 4-5)

N-[(2R,3R)-4-(N-(Benzyloxyamino)-2-isobutyl-3-[(3-pyridylcarbonyl)aminomethyl]succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -23.3° (c 0.24, 1N-HClaq.)

mp : 256-258°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.77-0.89 (1H, m), 0.80 (3H, d, J=7Hz), 1.28 (1H, m), 1.40 (1H, m), 2.33 (1H, ddd, J=9, 9, 4Hz), 2.44-2.55 (1H, m), 2.59 (3H, d, J=4.5Hz), 2.74-2.87 (1H, m), 2.85 (1H, dd, J=13, 10Hz), 2.90-3.03 (1H, m), 2.98 (1H, dd, J=13, 5Hz), 4.58 (1H, d, J=11Hz), 4.61 (1H, m), 4.73 (1H, d, J=11Hz), 7.21-7.31 (7H, m), 7.49 (1H, dd, J=7.5, 5Hz), 7.89 (1H, q, J=4.5Hz), 8.12 (1H, ddd, J=7.5, 1.5, 1.5Hz), 8.34-8.45 (2H, m), 8.37 (2H, d, J=6Hz), 8.69 (1H, dd, J=5, 1.5Hz), 8.95 (1H, d, J=1.5Hz), 11.04 (1H, s)

HPLC : 4.0 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=575

Example 4-6)

N-[(2R,3R)-4-(N-Benzyloxyamino)-2-isobutyl-3-[(4-pyridylcarbonyl)aminomethyl]succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -26.3° (c 0.24, 1N-HClaq.)

mp : 255-259°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.75-0.90 (1H, m), 0.80 (3H, d, J=7Hz). 1.28 (1H, m), 1.40 (1H, m), 2.33 (1H, m), 2.58 (3H, d, J=4.5Hz), 2.68-3.03 (5H, m), 4.58 (1H, d, J=11Hz), 4.61 (1H, m), 4.72 (1H, d, J=11Hz), 7.20-7.32 (7H, m), 7.68 (2H, d, J=6Hz), 7.88 (1H, q, J=4.5Hz), 8.37 (2H, d, J=6Hz), 8.41 (1H, d, J=8Hz), 8.48 (1H, dd, J=5, 5Hz), 8.70 (2H, d, J=6Hz), 11.04 (1H, s)

HPLC : 8.9 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 20:80, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=575

Example 4-7)

N-[(2R,3R)-4-(N-Benzyloxyamino)-2-isobutyl-3-[(6-methylpyridin-3-yl)carbonylaminomethyl]succinyl]-L-2-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -26.0° (c 0.05, 1N-HClaq.)

mp : 240-242°C (dec.)

HPLC : 3.0 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=485

Example 4-8)

N-[(2R,3R)-4-(N-Benzyloxyamino)-2-isobutyl-3-[(2-quinolinecarbonyl)aminomethyl]succinyl]-L-2-pyridylalanine

methylamide

HPLC : 17.3 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

Example 4-9)

N-[(2R,3R)-4-(N-Benzyloxyamino)-2-isobutyl-3-[3-quinolinecarbonyl)aminomethyl]succinyl]-L-2-pyridylalanine methylamide

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=6Hz), 0.81 (3H, d, J=6Hz), 0.84 (1H, m), 1.28 (1H, m), 1.43 (1H, m), 2.32-2.57 (2H, m), 2.59 (3H, d, J=5Hz), 2.80-2.90 (1H, m), 2.94-3.02 (1H, m), 3.03 (1H, dd, J=12, 9Hz), 3.14 (1H, dd, J=12, 6Hz), 4.58 (1H, d, J=11.3Hz), 4.76 (1H, d, J=11.3Hz), 4.78 (1H, m), 7.07 (1H, ddd, J=7.5, 6, 1.5Hz), 7.12-7.25 (5H, m), 7.30 (1H, dd, J=7.5, 1.5Hz), 7.63 (1H, ddd, J=7.5, 6, 1.5Hz), 7.70 (1H, dd, J=7.5, 1.5Hz), 7.74-7.80 (1H, m), 7.86 (1H, ddd, J=7.5, 6, 1.5Hz), 8.07 (2H, ddd, J=7.5, 6, 1.5Hz), 8.39-8.44 (2H, m), 8.37-8.46 (2H, m), 8.56-8.61 (1H, m), 8.77 (1H, d, J=1.5Hz), 9.25 (1H, d, J=1.5Hz)

HPLC : 6.3 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=625

Example 4-10)

N-[(2R,3R)-4-(N-Benzyloxyamino)-2-isobutyl-3-[(6-methylpyridin-2-yl)carbonylaminomethyl]succinyl]-L-2-pyridylalanine methylamide

HPLC : 7.9 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=589

Example 4-11)

N-[(2R,3R)-4-(N-Benzyloxyamino)-3-[(4-hydroxyquinolin-2-yl)carbonylaminomethyl]-2-isobutylsuccinyl]-L-2-pyridylalanine methylamide

HPLC : 5.9 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min. at R.T.)

MASS : M+H=641

Example 4-12)

N-[(2R,3R)-4-(N-Benzyloxyamino)-2-isobutyl-3-[(1-pyrrolidinylcarbonyl)aminomethyl]succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -17.2° (c 0.26, 1N-HClaq.)

mp : 213-216°C (dec.)

NMR (DMSO-d_6, δ) : 0.68 (3H, d, J=7Hz), 0.75 (3H, d, J=7Hz), 0.82 (1H, m), 1.19 (1H, m), 1.34 (1H, m), 1.66-1.82 (4H, m), 2.26 (1H, m), 2.44 (1H, m), 2.55 (3H, d, J=4.5Hz), 2.70-3.03 (4H, m), 3.05-3.24 (4H, m), 4.53 (1H, m), 4.70 (1H, d, J=11Hz), 4.80 (1H, d, J=11Hz), 5.67 (1H, br), 7.23 (2H, d, J=6Hz), 7.35 (5H, s), 7.85 (1H, q, J=4.5Hz), 8.31 (1H, d, J=8Hz), 8.40 (2H, d, J=6Hz), 10.95 (1H, s)

HPLC : 4.2 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=567

Example 4-13)

N-[(2R,3R)-4-(N-Benzyloxyamino)-2-isobutyl-3-[(3-pyridylcarbonyl)aminomethyl]succinyl]-L-2-pyridylalanine methylamide

HPLC : 3.1 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min. at R.T.)

Example 4-14)

N-[(2R,3R)-4-(N-Benzyloxyamino)-2-isobutyl-3-[(2-pyridylcarbonyl)aminomethyl]succinyl]-L-2-pyridylalanine methylamide

HPLC : 6.5 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

Example 5-1)

N-[(2R,3R)-4-(N-Benzyloxyamino)-2-isobutyl-3-[N-methyl-N-(2-quinolylcarbonyl)amino]methylsuccinyl]-L-2-pyridylalanine methylamide

HPLC : 3.9 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 40:60, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=639

Example 5-2)

N-[(2R,3R)-4-(N-Benzyloxyamino)-2-isobutyl-3-[N-methyl-N-[(6-methylpyridin-2-yl)carbonylamino]methylsuccinyl]-L-2-pyridylalanine methylamide

HPLC : 5.3 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min. at R.T.)

MASS : M+H=603

Example 5-3)

N-[(2R,3R)-4-(N-Benzyloxyamino)-2-isobutyl-3-[N-methyl-N-(3-pyridylcarbonyl)aminomethyl]succinyl]-L-2-pyridylalanine methylamide

NMR ($CDCl_3$, δ) : 0.79 (3H, d, J=6Hz), 0.86 (3H, d, J=6Hz), 0.86-1.50 (3H, m), 0.95 (1H, m), 2.72 (3H, d, J=5Hz), 2.96 (3H, s), 3.04-3.14 (4H, m), 3.17-3.39 (2H, m), 4.71-4.97 (3H, m), 7.12-8.69 (13H, m)

HPLC : 12.9 min. (Nucleosil 5C18, 4 mmϕ x 15 cm,

MeCN:0.05% TFAaq. = 20:80, 260 nm, flow rate 1.0 ml/min., at R.T.)

Example 5-4)

N-[(2R,3R)-4-(N-Benzyloxyamino)-2-isobutyl-3-[N-methyl-N-(2-pyridylcarbonyl)aminomethyl]succinyl]-L-2-pyridylalanine methylamide

HPLC : 6.3 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=589

Example 6-1)

N-[(2R,3R)-4-(N-Benzyloxyamino)-2-isobutyl-3-[3-(pyridin-3-yl)propionylaminomethyl]succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{25}$ = -47.9° (c 0.25, 1N-HClaq.)

mp : 249-253°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.73-0.89 (1H, m), 0.77 (3H, d, J=7Hz), 1.24 (1H, m), 1.37 (1H, m), 2.19 (1H, m), 2.24-2.35 (2H, m), 2.42 (1H, m), 2.56 (3H, d, J=5Hz), 2.64 (1H, m), 2.71-2.89 (4H, m), 2.96 (1H, dd, J=14, 5Hz), 4.58 (1H, m), 4.70 (1H, d, J=11Hz), 4.78 (1H, d, J=11Hz), 7.19-7.42 (6H, m), 7.23 (2H, d, J=6Hz), 7.52-7.64 (2H, m), 7.85 (1H, q, J=5Hz), 8.25-8.47 (3H, m), 8.37 (2H, d, J=6Hz), 11.02 (1H, s)

HPLC : 6.6 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 20:80, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=603

Example 6-2)

N-[(2R,3R)-4-(N-Benzyloxyamino)-2-isobutyl-3-[(3-pyridyl)acetamidomethyl]succinyl]-L-4-pyridylalanine

methylamide

$[\alpha]_D^{23}$ = -52.5° (c 0.22, 1N-HClaq.)

mp : 258-261°C (dec.)

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.73-0.87 (1H, m), 0.76 (3H, d, J=7Hz), 1.23 (1H, m), 1.37 (1H, m), 2.20 (1H, m), 2.42 (1H, m), 2.54 (3H, d, J=4.5Hz), 2.62-2.75 (2H, m), 2.81 (1H, dd, J=14, 11Hz), 2.95 (1H, dd, J=14, 5Hz), 3.35 (2H, d, J=6Hz), 4.56 (1H, m), 4.64 (1H, d, J=11Hz), 4.75 (1H, d, J=11Hz), 7.23 (2H, d, J=6Hz), 7.30 (1H, dd, J=7.5, 5Hz), 7.35 (5H, s), 7.62 (1H, m), 7.80-7.95 (2H, m), 8.27-8.46 (5H, m), 11.06 (1H, s)

HPLC : 5.9 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 20:80, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=589

Example 7

To a solution of N-[(2R,3R)-3-aminomethyl-4-(N-benzyloxyamino)-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide (413 mg) and N,N-diisopropyl-N-ethylamine (142 mg) in DMF (8 ml) was added N,N-dimethylcarbamoyl chloride (105 mg) at 0°C. The mixture was stirred at room temperature overnight. The solution was evaporated. The precipitate was collected by filtration and was washed with water and ethyl acetate. That solid was further purified by silica gel column chromatography (eluent : methanol/ethyl acetate=1/10) to give N-[(2R,3R)-4-(N-benzyloxyamino)-3-(N',N'-dimethylureido)methyl-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide (276 mg).

$[\alpha]_D^{23}$ = 23.2° (c 0.26, 1N-HClaq.)

mp : 209-211°C (dec.)

NMR (DMSO-d_6, δ) : 0.77 (3H, d, J=7Hz), 0.84 (3H, d, J=7Hz), 0.91 (1H, m), 1.18 (1H, m), 1.34 (1H, m),

2.27 (1H, m), 2.43 (1H, m), 2.55 (3H, d, J=4.5Hz), 2.67-3.03 (3H, m), 2.71 (6H, s), 2.98 (1H, dd, J=14, 5Hz), 4.52 (1H, m), 4.70 (1H, d, J=11Hz), 4.80 (1H, d, J=11Hz), 5.90 (1H, dd, J=5, 4Hz), 7.23 (2H, d, J=6Hz), 7.36 (5H, s), 7.85 (1H, q, J=4.5Hz), 8.32 (1H, d, J=8Hz), 8.40 (2H, d, J=6Hz), 10.95 (1H, s)

HPLC : 5.5 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=541

Example 8-1)

To a solution of N-[(2R,3R)-3-aminomethyl-4-(N-benzyloxyamino)-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide (380 mg) in DMF (3 ml) and pyridine (3 ml) were added acetic anhydride (103 mg) at room temperature. The mixture was stirred at room temperature for 2 hours. DMF was evaporated and the residue was poured into water. The precipitate was collected by filtration and washed with water and ethyl acetate to give N-[(2R,3R)-3-acetamidomethyl-4-(N-benzyloxyamino)-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide (367 mg).

$[\alpha]_D^{25}$ = -37.7° (c 0.28, 1N-HClaq.)

mp : 253-256°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.74-0.87 (1H, m), 0.78 (3H, d, J=7Hz), 1.25 (1H, m), 1.36 (1H, m), 1.70 (3H, s), 2.17 (1H, m), 2.41 (1H, m), 2.53-2.69 (1H, m), 2.56 (3H, d, J=4.5Hz), 2.76 (1H, m), 2.84 (1H, dd, J=14, 11Hz), 2.96 (1H, dd, J=14, 5Hz), 4.56 (1H, ddd, J=11, 8, 5Hz), 4.72 (1H, d, J=11Hz), 4.79 (1H, d, J=11Hz), 7.24 (2H, d, J=6Hz), 7.28-7.43 (5H, m), 7.53 (1H, dd, J=6, 6Hz), 7.86 (1H, q, J=4.5Hz), 8.31 (1H, d, J=8Hz), 8.38 (2H, d, J=6Hz), 11.00 (1H, s)

HPLC : 5.1 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=512

Example 8-2)

N-[(2R,3R)-4-(N-Benzyloxyamino)-2-isobutyl-3-(propionylaminomethyl)succinyl]-L-4-pyidylalanine methylamide was obtained in substantially the same manner as that of Example 8-1).

$[\alpha]_D^{25}$ = -49.7° (c 0.21, 1N-HClaq.)

mp : 245-247°C (dec.)

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.73-0.86 (1H, m), 0.77 (3H, d, J=7Hz), 0.93 (3H, t, J=7.5Hz), 1.23 (1H, m), 1.35 (1H, m), 1.97 (2H, q, J=7.5Hz), 2.17 (1H, m), 2.42 (1H, m), 2.55 (3H, d, J=5Hz), 2.60-2.90 (3H, m), 2.96 (1H, dd, J=13, 5Hz), 4.57 (1H, m), 4.70 (1H, d, J=11Hz), 4.78 (1H, d, J=11Hz), 7.24 (2H, d, J=6Hz), 7.28-7.52 (6H, m), 7.86 (1H, q, J=5Hz), 8.31 (1H, d, J=8Hz), 8.38 (2H, d, J=6Hz), 11.00 (1H, s)

HPLC : 6.4 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=526

Example 9

N-[(2R,3R)-4-(N-Benzyloxyamino)-3-(N,N-dimethylamino)-acetamidomethyl-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide was obtained in substantially the same manner as that of Example 4-1).

$[\alpha]_D^{23}$ = -56.3° (c 0.23, 1N-HClaq.)

mp : 243-248°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.74-0.87 (1H, m), 0.78 (3H, d, J=7Hz), 1.25 (1H, m), 1.35 (1H,

m), 2.16 (2x3H, s), 2.20 (1H, m), 2.44 (1H, m), 2.57 (3H, d, J=4.5Hz), 2.65 (1H, m), 2.75 (2H, s), 2.77-2.91 (2H, m), 2.95 (1H, dd, J=14, 5Hz), 4.55 (1H, m), 4.72 (1H, d, J=11Hz), 4.77 (1H, d, J=11Hz), 7.20-7.29 (3H, m), 7.36 (5H, s), 7.85 (1H, q, J=4.5Hz), 8.33-8.43 (3H, m), 11.07 (1H, s)

HPLC : 5.6 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 20:80, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=555

Example 10

N-[(2R,3R)-3-Benzamidomethyl-4-(N-benzyloxyamino)-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide was obtained in substantially the same manner as that of Example 4-1).

$[\alpha]_D^{25}$ = -15.8° (c 0.22, HCOOH)

mp : 243-247°C (dec.)

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=7Hz), 0.75-0.91 (1H, m), 0.80 (3H, d, J=7Hz), 1.26 (1H, m), 1.39 (1H, m), 2.36 (1H, m), 2.45-2.63 (1H, m), 2.57 (3H, d, J=5Hz), 2.76-2.90 (2H, m), 2.91-3.05 (2H, m), 4.57 (1H, d, J=11Hz), 4.60 (1H, m), 4.72 (1H, d, J=11Hz), 7.19-7.33 (7H, m), 7.38-7.54 (3H, m), 7.74-7.84 (2H, m), 7.88 (1H, q, J=5Hz), 8.14 (1H, br), 8.31-8.47 (3H, m), 10.99 (1H, s)

HPLC : 6.8 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=575

Example 11

To a solution of N-[(2R,3R)-3-aminomethyl-4-(N-benzyloxyamino)-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide (356 mg) in DMSO (6 ml) was added phenyl isocyanate (93 mg). The mixture was stirred at 50°C for 2

hours. The solvent was evaporated and the residue was poured into water. The precipitate was collected by filtration and washed with water and ethyl acetate to give N-[(2R,3R)-4-(N-benzyloxyamino)-2-isobutyl-3-[(N'-phenylureido)methyl]-succinyl]-L-4-pyridylalanine methylamide (409 mg).

$[\alpha]_D^{25}$ = -36.5° (c 0.19, HCOOH)

mp : 239-243°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.82 (1H, m), 1.24 (1H, m), 1.37 (1H, m), 2.25 (1H, m), 2.41 (1H, m), 2.57 (3H, d, J=5Hz), 2.70-2.92 (3H, m), 2.98 (1H, dd, J=14, 5Hz), 4.57 (1H, m), 4.74 (1H, d, J=11Hz), 4.80 (1H, d, J=11Hz), 5.91 (1H, br), 6.88 (1H, dd, J=7, 7Hz), 7.14-7.43 (11H, m), 7.85 (1H, q, J=5Hz), 8.31 (1H, d, J=8Hz), 8.35-8.47 (3H, m), 11.15 (1H, s)

HPLC : 7.9 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=589

Example 12-1)

To a solution of N-[(2R,3R)-4-(N-benzyloxyamino)-2-isobutyl-3-[(2-pyridylcarbonyl)aminomethyl]succinyl]-L-4-pyridylalanine methylamide (115 mg) in a mixture of cyclohexene (1 ml) and ethanol (20 ml) was added 10% palladium on carbon. The mixture was stirred under reflux for 2.5 hours. After the catalyst was filtered off, the filtrate was evaporated. The resulting residue was triturated with ethyl acetate to give N-[(2R,3R)-4-(N-hydroxyamino)-2-isobutyl-3-[(2-pyridylcarbonyl)aminomethyl]-succinyl]-L-4-pyridylalanine methylamide (91 mg).

mp : 239-242°C

NMR (DMSO-d_6, δ) : 0.74 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.91 (1H, m), 1.30 (1H, m), 1.41 (1H, m), 2.38 (1H, ddd, J=9, 9, 4Hz), 2.47-2.61 (1H, m),

2.57 (3H, d, J=4.5Hz), 2.80-2.91 (1H, m), 2.85 (1H, dd, J=14, 11Hz), 2.96 (1H, dd, J=14, 5Hz), 3.24 (1H, m), 4.57 (1H, ddd, J=11, 8, 5Hz), 7.25 (2H, d, J=7Hz), 7.60 (1H, dd, J=6, 6Hz), 7.87 (1H, q, J=4.5Hz), 7.95-8.06 (2H, m), 8.17 (1H, dd, J=5.5, 5.5Hz), 8.37 (2H, d, J=7Hz), 8.43 (1H, d, J=8Hz), 8.63 (1H, d, J=6Hz), 8.85 (1H, s), 10.50 (1H, s)

HPLC : 8.7 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 1:10, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=485

The following compounds were obtained in substantially the same manner as that of Example 12-1).

Example 12-2)

N-[(2R,3R)-4-(N-Hydroxyamino)-2-isobutyl-3-[(6-methylpyridin-3-yl)carbonylaminomethyl]succinyl]-L-4-pyridylalanine·methylamide

$[\alpha]_D^{25}$ = -37.4° (c 0.29, 1N-HClaq.)

mp : 237-242°C

NMR (DMSO-d_6, δ) : 0.74 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.91 (1H, ddd, 13, 3, 3Hz), 1.30 (1H, m), 1.41 (1H, m), 2.38 (1H, ddd, J=9, 9, 4Hz), 2.53 (3H, s), 2.58 (3H, d, J=4.5Hz), 2.80-2.91 (1H, m), 2.85 (1H, dd, J=14, 11Hz), 2.96 (1H, dd, J=14, 5Hz), 3.24 (1H, m), 4.57 (1H, ddd, J=11, 8, 5Hz), 7.25 (2H, d, J=7Hz), 7.45 (1H, br-d, J=7.5Hz), 7.78-7.91 (3H, m), 8.10 (1H, dd, J=5.5, 5.5Hz), 8.37 (2H, d, J=7Hz), 8.41 (1H, d, J=8Hz), 8.86 (1H, s), 10.51 (1H, s)

HPLC : 4.7 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 15:85, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=499

Example 12-3)

N-[(2R,3R)-4-(N-Hydroxyamino)-2-isobutyl-3-[(2-pyridylcarbonyl)aminomethyl]succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{25}$ = -30.1° (c 0.31, 1N-HClaq.)

mp : 240-242°C (dec.)

NMR (DMSO-d_6, δ) : 0.74 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.91 (1H, m), 1.29 (1H, m), 1.41 (1H, m), 2.38 (1H, ddd, J=9, 9, 4Hz), 2.48-2.61 (1H, m), 2.58 (3H, d, J=4.5Hz), 2.80-2.91 (1H, m), 2.85 (1H, dd, J=14, 11Hz), 2.96 (1H, dd, J=14, 5Hz), 3.24 (1H, m), 4.56 (1H, ddd, J=11, 8, 5Hz), 7.25 (2H, d, J=7Hz), 7.60 (1H, m), 7.86 (1H, q, J=4.5Hz), 7.96-8.05 (2H, m), 8.16 (1H, dd, J=6, 6Hz), 8.37 (2H, d, J=6Hz), 8.42 (1H, d, J=8Hz), 8.62 (1H, br d, J=5Hz), 8.85 (1H, s), 10.49 (1H, s)

HPLC : 9.4 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 1:10, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=485

Example 12-4)

N-[(2R,3R)-4-(N-Hydroxyamino)-2-isobutyl-3-[(3-pyridylcarbonyl)aminomethyl]succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{25}$ = -27.7° (c 0.20, 1N-HClaq.)

mp : 229-235°C

NMR (DMSO-d_6, δ) : 0.74 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.90 (1H, m), 1.27 (1H, m), 1.43 (1H, m), 2.35 (1H, ddd, J=9, 9, 4Hz), 2.43-2.55 (1H, m), 2.59 (3H, d, J=4.5Hz), 2.75 (1H, m), 2.84 (1H, dd, J=14, 12Hz), 2.92-3.08 (1H, m), 2.98 (1H, dd, J=14, 5Hz), 4.60 (1H, ddd, J=12, 8, 5Hz), 7.26 (2H, d, J=7Hz), 7.49 (1H, dd, J=7.5, 5Hz), 7.88 (1H, q, J=4.5Hz), 8.10 (1H, ddd, J=7.5, 1.5, 1.5Hz), 8.23

(1H, dd, J=6, 6Hz), 8.47 (2H, d, J=6Hz), 8.50 (1H, d, J=8Hz), 8.68 (1H, dd, J=5, 5Hz), 8.73 (1H, s), 8.92 (1H, d, J=1.5Hz), 10.35 (1H, s)

HPLC : 4.7 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min. at R.T.)

MASS : M+H=485

Example 12-5)

To a solution of N-[(2R,3R)-4-(N-benzyloxyamino)-2-isobutyl-3-[(4-pyridylcarbonyl)aminomethyl]succinyl]-L-4-pyridylalanine methylamide (375 mg) in a mixture of cyclohexene (2 ml), formic acid (3.5 ml) and ethanol (20 ml) was added 5% palladium on barium sulfate. The mixture was stirred under reflux for 12 hours. After the catalyst was filtered off, the filtrate was evaporated. The resulting residue was triturated with ethyl acetate to give N-[(2R,3R)-4-(N-hydroxyamino)-2-isobutyl-3-(4-pyridylcarbonyl)-aminomethylsuccinyl]-L-4-pyridylalanine methylamide (16 mg).

$[\alpha]_D^{23}$ = -27.6° (c 0.30, 1N-HClaq.)

mp : 243-248°C (dec.)

NMR (DMSO-d_6, δ) : 0.74 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.90 (1H, m), 1.28 (1H, m), 1.42 (1H, m), 2.35 (1H, ddd, J=9, 9, 3Hz), 2.45-2.55 (1H, m), 2.58 (3H, d, J=4.5Hz), 2.76 (1H, m), 2.84 (1H, dd, J=14, 11Hz), 2.92-3.08 (1H, m), 2.97 (1H, dd, J=14, 5Hz), 4.60 (1H, ddd, J=11, 8, 5Hz), 7.26 (2H, d, J=7Hz), 7.49 (1H, dd, J=7.5, 5Hz), 7.88 (1H, q, J=4.5Hz), 8.10 (1H, ddd, J=7.5, 1.5, 1.5Hz), 8.22 (1H, dd, J=5.5, 5.5Hz), 8.37 (2H, d, J=7Hz), 8.40 (1H, d, J=8Hz), 8.69 (1H, dd, J=5, 1.5Hz), 8.75 (1H, s), 8.92 (1H, d, J=1.5Hz), 10.36 (1H, s)

HPLC : 4.0 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 1:10, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=485

The following compounds were obtained in substantially the same manner as that of Example 12-5).

Example 12-6)

N-[(2R,3R)-4-(N-Hydroxyamino)-2-isobutyl-3-[(4-pyridylcarbonyl)aminomethyl]succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -30.2° (c 0.34, 1N-HClaq.)

mp : 244-248°C (dec.)

NMR (DMSO-d_6, δ) : 0.75 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.89 (1H, m), 1.28 (1H, m), 1.43 (1H, m), 2.35 (1H, m), 2.43-2.54 (1H, m), 2.59 (3H, d, J=5Hz), 2.72 (1H, m), 2.84 (1H, dd, J=14, 12Hz), 2.91-3.08 (2H, m), 4.60 (1H, m), 7.25 (2H, d, J=6Hz), 7.67 (2H, d, J=6Hz), 7.88 (1H, q, J=5Hz), 8.25-8.44 (4H, m), 8.65-8.78 (3H, m), 10.35 (1H, s)

HPLC : 4.5 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 1:10, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=485

Example 12-7)

N-[(2R,3R)-4-(N-Hydroxyamino)-2-isobutyl-3-[3-(pyridin-3-yl)propionylaminomethyl]succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{25}$ = -23.3° (c 0.30, 1N-HClaq.)

mp : 241-246°C (dec.)

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz), 0.86 (1H, m), 1.23 (1H, m), 1.38 (1H, m), 2.21 (1H, m), 2.31 (2H, t, J=7Hz), 2.40 (1H, m), 2.55 (3H, d, J=5Hz), 2.61-2.89 (5H, m), 2.95 (1H, dd, J=13, 4Hz), 4.55 (1H, m), 7.23 (2H, d, J=6Hz),

7.30 (1H, dd, J=7.5, 5Hz), 7.46 (1H, dd, J=6, 6Hz), 7.60 (1H, m), 7.85 (1H, q, J=5Hz), 8.30 (1H, d, J=8Hz), 8.34-8.44 (4H, m), 8.78 (1H, s), 10.35 (1H, s)

HPLC : 3.9 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 1:10, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=513

Example 12-8)

N-[(2R,3R)-4-(N-Hydroxyamino)-2-isobutyl-3-[(3-pyridylacetamido)methyl]succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{25}$ = -35.2° (c 0.24, 1N-HClaq.)

mp : 230-236°C (dec.)

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.86 (1H, m), 1.23 (1H, m), 1.38 (1H, m), 2.21 (1H, m), 2.41 (1H, m), 2.55 (3H, d, J=4Hz), 2.61-2.88 (3H, m), 2.95 (1H, dd, J=13, 4Hz), 3.37 (2H, s), 4.55 (1H, m), 7.22 (2H, d, J=6Hz), 7.31 (1H, m), 7.64 (1H, m), 7.77 (1H, m), 7.84 (1H, q, J=4Hz), 8.29 (1H, d, J=8Hz), 8.34 (2H, d, J=6Hz), 8.37-8.45 (2H, m), 8.67 (1H, s), 10.38 (1H, s)

HPLC : 3.6 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 1:10, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=499

Example 12-9)

N-[(2R,3R)-3-(N,N-Dimethylamino)acetamidomethyl-4-(N-hydroxyamino)-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -29.5° (c 0.26, 1N-HClaq.)

mp : 230-235°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.78 (3H, d,

J=7Hz), 0.87 (1H, m), 1.26 (1H, m), 1.38 (1H, m), 2.11 (1H, m), 2.13 (2x3H, s), 2.33 (1H, m), 2.58 (3H, d, J=4Hz), 2.63 (1H, m), 2.76-3.01 (5H, m), 4.55 (1H, m), 7.25 (2H, d, J=6Hz), 7.25 (1H, m), 7.86 (1H, q, J=4Hz), 8.35 (1H, d, J=8Hz), 8.39 (2H, d, J=6Hz), 8.80 (1H, s), 10.44 (1H, s)

HPLC : 3.6 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 1:10, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=465

Example 12-10)

N-[(2R,3R)-4-(N-Hydroxyamino)-2-isobutyl-3-[3-(6-methylpiridin-3-yl)carbonylaminomethyl]succinyl]-L-2-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -37.9° (c 0.14, 1N-HClaq.)

mp : 204-207°C

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=6Hz), 0.78 (3H, d, J=6Hz), 0.88 (1H, ddd, J=12, 9, 1.5Hz), 1.24 (1H, m), 1.43 (1H, ddd, J=12, 9, 1.5Hz), 2.32-2.49 (2H, m), 2.50 (3H, s), 2.57 (3H, d, J=5Hz), 2.70-2.80 (1H, m), 2.93-3.02 (1H, m), 3.00 (1H, dd, J=12, 9Hz), 3.11 (1H, dd, J=12, 6Hz), 4.76 (1H dd, J=9, 6Hz), 7.06 (1H, ddd, J=7.5, 6, 1.5Hz), 7.26 (1H, d, J=7.5Hz), 7.32 (1H, d, J=7.5Hz), 7.60 (1H, ddd, J=7.5, 6, 1.5Hz), 7.73-7.80 (1H, m), 8.00 (1H, dd, J=7.5, 1.5Hz), 8.18 (1H, br s), 8.37-8.44 (2H, m), 8.82 (1H, d, J=1.5Hz)

HPLC : 8.6 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 1:10, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=499

Example 12-11)

N-[(2R,3R)-4-(N-Hydroxyamino)-2-isobutyl-3-[(2-quinolinecarbonyl)aminomethyl]succinyl]-L-2-pyridylalanine

methylamide

$[\alpha]_D^{23}$ = -60.0° (c 0.10, 1N-HClaq.)

mp : 232-236°C

NMR (DMSO-d_6, δ) : 0.74 (3H, d, J=6Hz), 0.80 (3H, d, J=6Hz), 0.86 (1H, m), 1.28 (1H, m), 1.46 (1H, m), 2.42 (2H, m), 2.61 (3H, d, J=5Hz), 2.85-3.30 (4H, m), 4.80 (1H, m), 7.50-8.74 (13H, m)

HPLC : 3.1 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=535

Example 12-12)

N-[(2R,3R)-4-(N-Hydroxyamino)-2-isobutyl-3-[(2-quinolinecarbonyl)aminomethyl]succinyl]-L-2-pyridylalanine methylamide

$[\alpha]_D^{25}$ = -35.6° (c 0.09, 1N-HClaq.)

mp : 244-246°C

NMR (DMSO-d_6, δ) : 0.74 (3H, d, J=6Hz), 0.80 (3H, d, J=6Hz), 0.91 (1H, m), 1.27 (1H, m), 1.45 (1H, m), 2.36-2.56 (2H, m), 2.59 (3H, d, J=5Hz), 2.76-3.06 (2H, m), 3.04 (1H, dd, J=12, 9Hz), 3.14 (1H, dd, J=12, 6Hz), 4.79 (1H, m), 7.07 (1H, ddd, J=7.5, 6, 1.5Hz), 7.29 (1H, dd, J=7.5, 1.5Hz), 7.62 (1H, ddd, J=7.5, 6, 1.5Hz), 7.70 (1H, dd, J=7.5, 1.5Hz), 7.74-7.80 (1H, m), 7.86 (1H, ddd, J=7.5, 6, 1.5Hz), 8.05-8.10 (2H, m), 8.36-8.46 (2H, m), 8.72-8.80 (2H, m), 9.23 (1H, s)

HPLC : 3.5 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 20:80, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=535

Example 12-13)

N-[(2R,3R)-4-(N-Hydroxyamino)-2-isobutyl-3-[N-methyl-N-

(2-quinolylcarbonyl)amino]methylsuccinyl]-L-2-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -37.5° (c 0.12, 1N-HClaq.)

mp : 203-205°C

NMR (CD_3OD, δ) : 0.69-0.94 (6H, m), 1.03-1.48 (3H, m), 2.25-2.61 (2H, m), 2.65 (0.5x3H, s, rotamer), 2.75 (0.5x3H, s, rotamer), 2.83 (0.5x3H, s, rotamer), 2.95 (0.5x3H, s, rotamer), 2.97-3.65 (4H, m), 4.67-4.96 (1H, m), 7.27-8.66 (10H, m)

HPLC : 7.2 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 20:80, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=485

Example 12-14)

N-[(2R,3R)-4-(N-Hydroxyamino)-2-isobutyl-3-[(6-methylpyridin-2-yl)carbonylaminomethyl]succinyl]-L-2-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -42.9° (c 0.14, 1N-HClaq.)

mp : 248-252°C

NMR (DMSO-d_6, δ) : 0.74 (3H, d, J=6Hz), 0.78 (3H, d, J=6Hz), 0.90 (1H, ddd, J=12, 9, 1.5Hz), 1.28 (1H, m), 1.43 (1H, ddd, J=12, 9, 1.5Hz), 2.31-2.52 (2H, m), 2.54 (3H, s), 2.57 (3H, d, J=5Hz), 2.85 (1H, m), 3.03 (1H, dd, J=12, 9Hz), 3.13 (1H, dd, J=12, 6Hz), 3.21 (1H, m), 4.73 (1H, dd, J=9, 6Hz), 7.05 (1H, ddd, J=7.5, 6, 1.5Hz), 7.26 (1H, dd, J=7.5, 1.5Hz), 7.45 (1H, dd, J=7.5, 1.5Hz), 7.57-7.89 (4H, m), 8.11 (1H, m), 8.35-8.43 (2H, m), 8.86 (1H, s)

HPLC : 22.5 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 1:10, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=499

Example 12-15)

N-[(2R,3R)-4-(N-Hydroxyamino)-2-isobutyl-3-[N-methyl-N-[(6-methylpyridin-2-yl)carbonyl]aminomethyl]succinyl]-L-2-pyridyalanine methylamide

$[\alpha]_D^{23}$ = -40.0° (c 0.14, 1N-HClaq.)

mp : 196-198°C

NMR (CD_3OD, δ) : 0.74-0.90 (6H, m), 1.06 (1H, m), 1.35 (1H, m), 1.48 (1H, m), 2.35-2.57 (2H, m), 2.59 (0.5x3H, d, J=5Hz, rotamer), 2.68 (3H, s), 2.73 (0.5x3H, d, J=5Hz, rotamer), 2.89 (3H, s), 3.00-3.40 (4H, m), 4.67-4.95 (1H, m), 7.18-8.54 (7H, m)

HPLC : 14.4 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 1:10, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=513

Example 12-16)

N-[(2R,3R)-4-(N-Hydroxyamino)-3-[(4-hydroxyquinolin-2-yl)carbonylaminomethyl]-2-isobutylsuccinyl]-L-2-pyridylalanine methylamide

mp : 209-211°C (dec.)

NMR ($DMSO-d_6$, δ) : 0.68-1.02 (7H, m), 1.30 (1H, m), 1.45 (1H, m), 2.27-2.84 (5H, m), 2.95-3.30 (4H, m), 4.77 (1H, m), 6.23 (1H, m), 7.07 (1H, m), 7.20-7.35 (2H, m), 7.50-7.67 (2H, m), 7.70-7.90 (2H, m), 8.07 (1H, m), 8.32-8.50 (3H, m), 8.82 (1H, br)

HPLC : 4.2 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 20:80, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=551

Example 12-17)

N-[(2R,3R)-3-(N',N'-Dimethylureido)methyl-4-(N-hydroxyamino)-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -26.3° (c 0.26, 1N-HClaq.)

mp : 200-204°C (dec.)

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.75 (3H, d, J=7Hz), 0.87 (1H, m), 1.20 (1H, m), 1.37 (1H, m), 2.30 (1H, m), 2.44 (1H, m), 2.57 (3H, d, J=5Hz), 2.68-3.04 (4H, m), 2.73 (2x3H, s), 4.51 (1H, m), 5.67 (1H, dd, J=5, 5Hz), 7.24 (2H, d, J=6Hz), 7.86 (1H, q, J=4.5Hz), 8.32 (1H, d, J=8Hz), 8.40 (2H, d, J=6Hz), 8.77 (1H, s), 10.29 (1H, s)

HPLC : 5.3 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 1:10, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=451

Example 12-18)

N-[(2R,3R)-4-(N-Hydroxyamino)-2-isobutyl-3-[(1-pyrrolidinylcarbonyl)aminomethyl]succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -21.4° (c 0.31, 1N-HClaq.)

mp : 216-219°C

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.76 (3H, d, J=7Hz), 0.88 (1H, m), 1.19 (1H, m), 1.37 (1H, m), 1.71-1.85 (4H, m), 2.28 (1H, m), 2.45 (1H, m), 2.56 (3H, d, J=4.5Hz), 2.76 (1H, m), 2.87 (1H, dd, J=14, 11Hz), 2.92-3.05 (2H, m), 3.08-3.26 (4H, m), 4.52 (1H, m), 5.42 (1H, dd, J=6, 5Hz), 7.24 (2H, d, J=7Hz), 7.87 (1H, q, J=4.5Hz), 8.32 (1H, d, J=8Hz), 8.41 (2H, d, J=7Hz), 8.77 (1H, s), 10.30 (1H, s)

HPLC : 3.4 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 15:85, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=477

Example 12-19)

N-[(2R,3R)-3-Benzamidomethyl-4-(N-hydroxyamino)-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{25}$ = -30.1° (c 0.23, 1N-HClaq.)

mp : 238-242°C (dec.)

NMR (DMSO-d_6, δ) : 0.74 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.90 (1H, m), 1.27 (1H, m), 1.43 (1H, m), 2.40 (1H, m), 2.45-2.63 (1H, m), 2.58 (3H, d, J=4Hz), 2.75-3.14 (4H, m), 4.58 (1H, m), 7.21-7.30 (2H, m), 7.38-7.57 (3H, m), 7.77 (2H, d, J=7Hz), 7.88 (1H, q, J=4Hz), 7.95 (1H, br), 8.32-8.45 (3H, m), 8.74 (1H, s), 10.35 (1H, s)

HPLC : 5.1 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 15:85, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=484

Example 12-20)

N-[(2R,3R)-4-(N-Hydroxyamino)-2-isobutyl-3-[(3-pyridylcarbonyl)aminomethyl]succinyl]-L-2-pyridylalanine methylamide

$[\alpha]_D^{25}$ = -35.2° (c 0.17, 1N-HClaq.)

mp : 220-223°C

NMR (DMSO-d_6, δ) : 0.74 (3H, d, J=6Hz), 0.79 (3H, d, J=6Hz), 0.89 (1H, ddd, J=12, 9, 1.5Hz), 1.25 (1H, m), 1.43 (1H, ddd, J=12, 9, 1.5Hz), 2.31-2.50 (2H, m), 2.57 (3H, d, J=5Hz), 2.72-2.82 (1H, m), 2.93-3.02 (1H, m), 3.00 (1H, dd, J=12, 9Hz), 3.11 (1H, dd, J=12, 6Hz), 4.75 (1H, dd, J=9, 6Hz), 7.07 (1H, ddd, J=7.5, 6, 1.5Hz), 7.18 (1H, dd, J=7.5, 1.5Hz), 7.49 (1H, dd, J=7.5, 6Hz), 7.61 (1H, ddd, J=7.5, 6, 1.5Hz), 7.76-7.83 (1H, m), 8.12 (1H, dd, J=7.5, 1.5Hz), 8.33 (1H, br s), 8.37-8.46 (2H, m), 8.68 (1H, d, J=6Hz), 8.93 (1H, s)

HPLC : 6.7 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 1:10, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=485

Example 12-21)

N-[(2R,3R)-4-(N-Hydroxyamino)-2-isobutyl-3-[(2-pyridylcarbonyl)aminomethyl]succinyl]-L-2-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -42.3° (c 0.04, 1N-HClaq.)

mp : 265-268°C

NMR (0.5N-DCl, δ) : 0.52-0.60 (6H, m), 0.83 (1H, m), 0.95 (1H, m), 1.26 (1H, m), 2.33-2.40 (2H, m), 2.46 (3H, s), 2.65 (1H, m), 3.13 (1H, m), 3.23-3.43 (2H, m), 7.63-8.73 (8H, m)

HPLC : 3.1 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 20:80, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=485

Example 12-22)

N-[(2R,3R)-4-(N-Hydroxyamino)-2-isobutyl-3-[N-methyl-N-(3-pyridylcarbonyl)aminomethyl]succinyl]-L-2-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -46.0° (c 0.05, 1N-HClaq.)

mp : 125-128°C

NMR (CD_3OD, δ) : 0.78-0.95 (6H, m), 1.08 (1H, m), 1.38 (1H, m), 1.58 (1H, m), 2.46-2.65 (2H, m), 2.72 (0.3x3H, br s, minor rotamer), 2.76 (0.7x3H, br s, major rotamer), 2.83 (0.7x3H, br s, major rotamer), 2.93 (0.3x3H, br s, minor rotamer), 3.04-3.33 (4H, m), 3.17-3.39 (2H, m), 4.87 (1H, m), 7.25-8.70 (8H, m)

HPLC : 6.1 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 1:10, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=499

Example 12-23)

N-[(2R,3R)-4-(N-Hydroxyamino)-2-isobutyl-3-[N-methyl-N-

(2-pyridylcarbonyl)amino]methylsuccinyl]-L-2-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -35.8° (c 0.12, 1N-HClaq.)

mp : 208-211°C

NMR (CD_3OD, δ) : 0.76-0.91 (6H, m), 1.05 (1H, m), 1.36 (1H, m), 1.54 (1H, m), 2.36 (1H, m), 2.56 (1H, m), 2.68 (0.5x3H, s, rotamer), 2.73 (0.5x3H, s, rotamer), 2.76 (0.5x3H, s, rotamer), 2.90 (0.5x3H, s, rotamer), 3.00-3.42 (4H, m), 4.67-4.96 (1H, m), 7.24-8.64 (8H, m)

HPLC : 10.5 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 1:10, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=499

Example 12-24)

N-[(2R,3R)-3-Acetamidomethyl-4-(N-hydroxyamino)-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{25}$ = -30.5°C (c 0.30, 1N-HClaq.)

mp : 246-250°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz), 0.85 (1H, m), 1.23 (1H, m), 1.38 (1H, m), 1.71 (3H, s), 2.18 (1H, m), 2.41 (1H, m), 2.56 (3H, d, J=5Hz), 2.65-2.75 (2H, m), 2.83 (1H, dd, J=14, 11Hz), 2.95 (1H, dd, J=14, 6Hz), 4.55 (1H, ddd, J=11, 8, 6Hz), 7.23 (2H, d, J=6Hz), 7.37 (1H, dd, J=6, 6Hz), 7.85 (1H, q, J=5Hz), 8.30 (1H, d, J=8Hz), 8.38 (2H, d, J=6Hz), 8.73 (1H, s), 10.33 (1H, s)

HPLC : 4.3 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 1:10, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=422

Example 12-25)

N-[(2R,3R)-4-(N-Hydroxyamino)-2-isobutyl-3-(propionylaminomethyl)succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -32.6° (c 0.30, 1N-HClaq.)

mp : 238-241°C (dec.)

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz), 0.85 (1H, m), 0.96 (3H, t, J=7Hz), 1.23 (1H, m), 1.38 (1H, ddd, J=11, 11, 3Hz), 1.97 (2H, q, J=7Hz), 2.20 (1H, m), 2.41 (1H, m), 2.56 (3H, d, J=5Hz), 2.62-2.90 (3H, m), 2.96 (1H, dd, J=14, 5Hz), 4.55 (1H, m), 7.25 (2H, d, J=6Hz), 7.28 (1H, m), 7.86 (1H, q, J=5Hz), 8.30 (1H, d, J=8Hz), 8.37 (2H, d, J=6Hz), 8.72 (1H, s), 10.31 (1H, s)

HPLC : 4.7 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 1:10, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=436

Example 12-26)

N-[(2R,3R)-4-(N-Hydroxyamino)-2-isobutyl-3-[(N'-phenylureido)methyl]succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{25}$ = -36.7° (c 0.28, 1N-HClaq.)

mp : 250-254°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.90 (1H, m), 1.25 (1H, m), 1.42 (1H, m), 2.25 (1H, m), 2.40 (1H, m), 2.57 (3H, d, J=5Hz), 2.77-2.92 (3H, m), 2.98 (1H, dd, J=14, 6Hz), 4.57 (1H, m), 5.81 (1H, dd, J=6, 4Hz), 6.87 (1H, dd, J=7, 7Hz), 7.15-7.28 (4H, m), 7.36 (2H, d, J=7.5Hz), 7.85 (1H, q, J=5Hz), 8.30 (1H, d, J=8Hz), 8.40 (2H, d, J=6Hz), 8.46 (1H, s), 8.85 (1H, s), 10.54 (1H, s)

HPLC : 3.6 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 20:80, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=499

Example 13

N-[(2R,3R)-3-Aminomethyl-4-(N-benzyloxyamino)-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide (1.73 g) was dissolved in water (15 ml) and the pH was adjusted to 8-9 by the addition of sodium hydrogen carbonate. The precipitate was collected by filtration to give N-[(2R,3R)-[3-aminomethyl-4-(N-benzyloxyamino)-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide (1.02 g).

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.73-0.88 (1H, m), 0.77 (3H, d, J=7Hz), 1.15-1.40 (2H, m), 1.85-2.00 (2H, m), 2.23 (1H, m), 2.41 (1H, m), 2.56 (3H, d, J=4.5Hz), 2.79 (1H, dd, J=14, 12Hz), 2.94 (1H, dd, J=14, 4Hz), 4.55 (1H, ddd, J=12, 8, 4Hz), 4.76 (2H, s), 7.25 (2H, d, J=6Hz), 7.28-7.44 (5H, m), 7.85 (1H, q, J=4.5Hz), 8.29 (1H, d, J=8Hz), 8.44 (2H, d, J=6Hz)

MASS : M+H=470

Example 14

N-[(2R,3R)-4-Benzyloxyamino-2-isobutyl-3-phthalimidomethylsuccinyl]-L-3-pyridylalanine methyl ester was obtained in substantially the same manner as that of Example 1-1).

$[\alpha]_D^{25}$ = -6.3° (c 0.20, AcOH)

mp : 214-219°C (dec.)

NMR (DMSO-d_6, δ) : 0.70-0.85 (1H, m), 0.75 (3H, d, J=6.5Hz), 0.80 (3H, d, J=6.5Hz), 1.30-1.46 (2H, m), 2.40 (1H, ddd, J=11, 10, 3Hz), 2.46-2.61 (1H, m), 2.90 (1H, dd, J=14, 11Hz), 3.17 (1H, dd, J=14, 5Hz), 3.50 (1H, dd, J=13, 11Hz), 3.62 (3H, s), 4.25 (1H, d, J=11Hz), 4.54 (1H, d, J=11Hz), 4.67 (1H, ddd, J=11, 8, 5Hz), 7.05 (2x1H, d, J=7.5Hz), 7.12-7.28 (4H, m), 7.70 (1H, br d, J=7.5Hz), 7.85 (4H,

m), 8.13 (1H, d, J=5Hz), 8.46 (1H, br), 8.65 (1H, d, J=7.5Hz), 11.06 (1H, s)

HPLC : 5.5 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 35:65, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=601

Example 15

N-[(2R,3R)-3-Aminomethyl-4-benzyloxyamino-2-isobutylsuccinyl]-L-3-pyridylalanine methylamide was obtained in substantially the same manner as that of Example 2-1).

$[\alpha]_D^{23}$ = -35.5° (c 0.31, 1N-HClaq.)

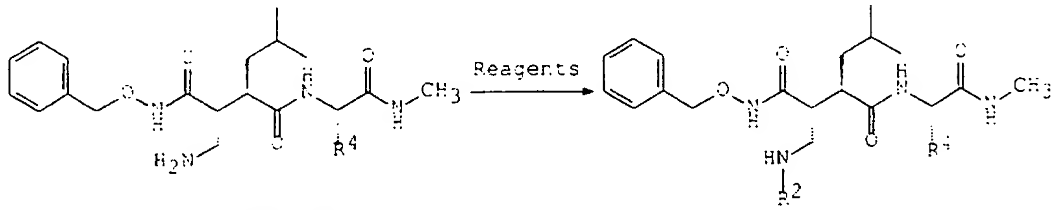
mp : 198-201°C (dec.)

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.73-0.88 (1H, m), 0.78 (3H, d, J=7Hz), 1.17-1.39 (2H, m), 1.78-1.97 (2H, m), 2.21 (1H, dd, J=13, 3Hz), 2.40 (1H, m), 2.56 (3H, d, J=4.5Hz), 2.79 (1H, dd, J=14, 11Hz), 2.94 (1H, dd, J=14, 4Hz), 4.36 (2H, br), 4.51 (1H, ddd, J=11, 8, 4Hz), 4.75 (1H, d, J=11Hz), 4.79 (1H, d, J=11Hz), 7.25-7.43 (5H, m), 7.29 (1H, dd, J=7.5, 5Hz), 7.65 (1H, br d, J=7.5Hz), 7.88 (1H, q, J=4.5Hz), 8.30 (1H, d, J=8Hz), 8.40 (1H, d, J=5Hz), 8.46 (1H, d, J=1.5Hz)

HPLC : 5.5 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:H_2O:TFA = 20:80:0.05, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=470

The Object Compounds listed in the following Table 1 were prepared, in substantially the same manner as that of Example 4-1), by reacting the Starting Compounds with the Reagent as shown below.



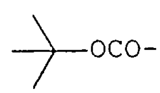
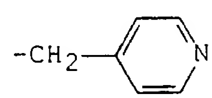
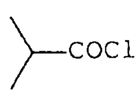
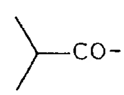
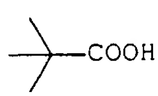
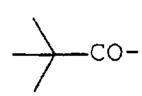
Starting Compounds

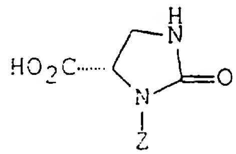
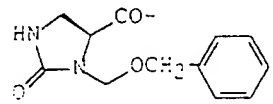
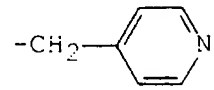
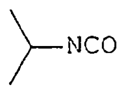
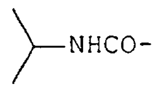
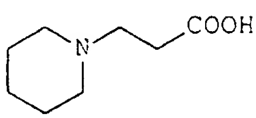
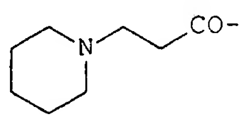
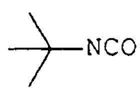
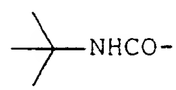
Object Compounds

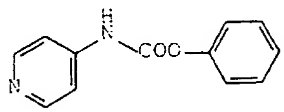
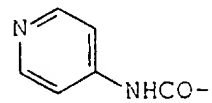
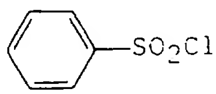
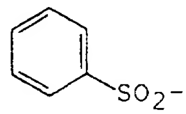
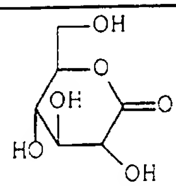
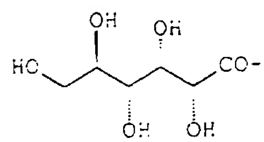
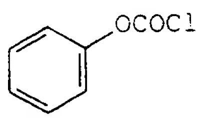
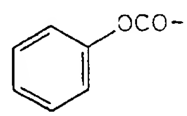
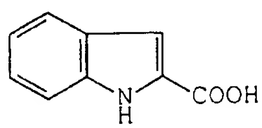
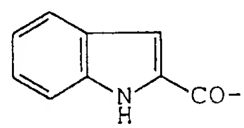
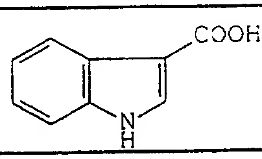
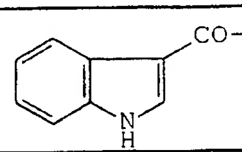
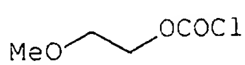
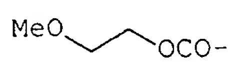
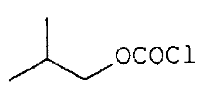
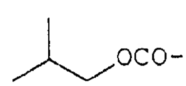
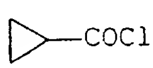
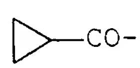
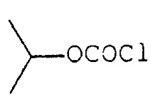
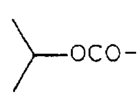
The abbreviations used in Table 1 are as follows.

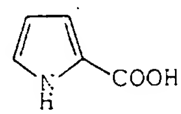
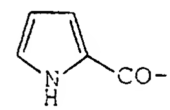
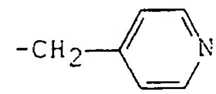
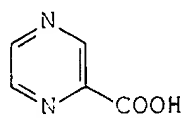
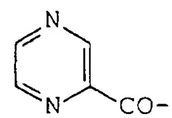
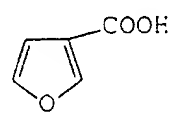
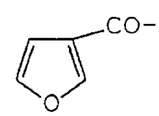
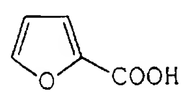
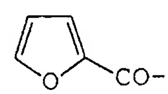
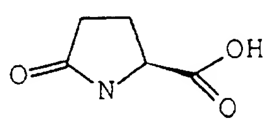
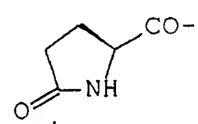
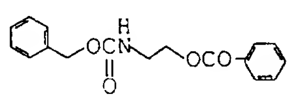
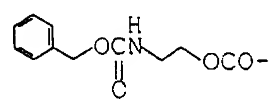
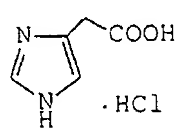
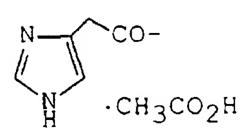
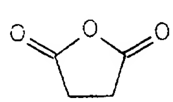
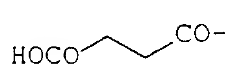
Me : methyl
Et : ethyl
Ac : acetyl
Z : benzyloxycarbonyl
Boc : t-butoxycarbonyl
gly : glycine residue
Ser : Serine residue

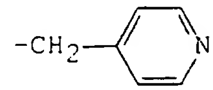
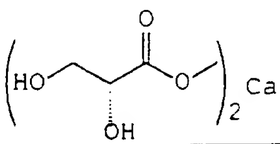
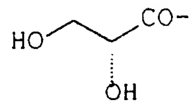
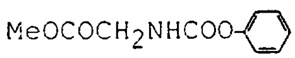
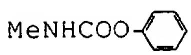
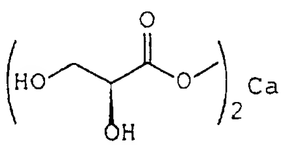
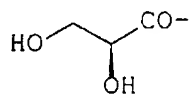
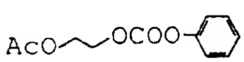
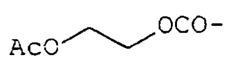
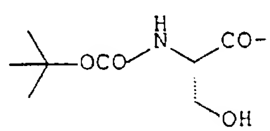
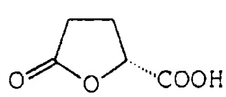
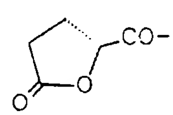
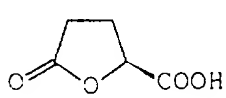
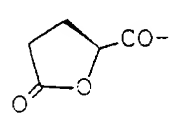
Table 1

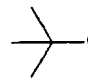
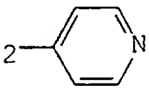
Example No.	Reagents	Object Compounds	
		R^2	R^4
16-1)	$(Boc)_2O$		
-2)			"
-3)			"
-4)	EtOCOCl	EtOCO-	"

Example No.	Reagents	Object Compounds	
		R^2	R^4
16-5)			
-6)	EtO_2CCH_2COCl	$EtOCOCH_2CO$-	"
-7)			"
-8)	EtNCO	EtNHCO-	"
-9)			"
-10)			"
-11)	$AcOCH_2COOH$	$AcOCH_2CO$-	"
-12)	MeOCOCl	MeOCO-	"
-13)	$MeOCH_2COCl$	$MeOCH_2CO$-	"
-14)	$MeSO_2Cl$	$MeSO_2$-	"

Example No.	Reagents	Object Compounds	
		R^2	R^4
16-15)			
-16)			"
-17)			"
-18)			"
-19)			"
-20)			"
-21)			"
-22)			"
-23)			"
-24)			"

Example No.	Reagents	Object Compounds	
		R^2	R^4
16-25)			
-26)			"
-27)	$EtSO_2Cl$	$EtSO_2$-	"
-28)			"
-29)			"
-30)	$(CF_3CO)_2O$	CF_3CO-	"
-31)			"
-32)			"
-33)			"
-34)			"

Example No.	Reagents	Object Compounds	
		R^2	R^4
16-35)		$AcNHCH_2CO-$	
-36)			"
-37)		$MeOCOCH_2NHCO-$	"
-38)		MeNHCO-	"
-39)			"
-40)	$MeSO_2CH_2COOH$	$MeSO_2CH_2CO-$	"
-41)			"
-42)	Boc-Ser		"
-43)			"
-44)			"

Example No.	Reagents	Object Compounds	
		R^2	R^4
16-45)	Boc-Gly-OH	$OCONHCH_2CO$-	$-CH_2-$
-46)	$H_2NCOCOOH$	H_2NCOCO-	"
-47)	$MeSO_2Cl$	$MeSO_2$-	"
-48)	$AcOCH_2COOH$	$AcOCH_2CO$-	"
-49)	EtOCOCl	EtOCO-	"

The physico-chemical properties of the Object Compounds of Table 1 were described hereinafter.

Example 16-1)

$[\alpha]_D^{24}$ = -14.6° (c 0.21, 1N-HClaq.)

mp : 229-232°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.73-0.87 (1H, m), 0.79 (3H, d, J=7Hz), 1.18-1.42 (2H, m), 1.35 (3x3H, s), 2.13 (1H, m), 2.45 (1H, m), 2.47-2.60 (1H, m), 2.57 (3H, d, J=4.5Hz), 2.65 (1H, m), 2.81 (1H, dd, J=14, 11Hz), 2.94 (1H, dd, J=14, 5Hz), 4.55 (1H, ddd, J=11, 8, 5Hz), 4.71 (1H, d, J=11Hz), 4.77 (1H, d, J=11Hz), 6.32 (1H, dd, J=5, 5Hz), 7.25 (2x1H, d, J=7Hz), 7.30-7.43 (5H, m), 7.85 (1H, q, J=4.5Hz), 8.36 (1H, d, J=8Hz), 8.40 (2x1H, d, J=6Hz), 10.95 (1H, s)

HPLC : 7.3 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:H_2O:TFA = 30:70:0.05, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=570

Example 16-2)

$[\alpha]_D^{25}$ = -53.9° (c 0.20, 1N-HClaq.)

mp : 263-267°C (dec.)

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.73-0.87 (1H, m), 0.78 (3H, d, J=7Hz), 0.94 (3H, d, J=7Hz), 0.95 (3H, d, J=7Hz), 1.23 (1H, m), 1.37 (1H, m), 2.11-2.33 (2H, m), 2.42 (1H, m), 2.53-2.78 (2H, m), 2.57 (3H, d, J=5Hz), 2.83 (1H, dd, J=13, 11Hz), 2.97 (1H, dd, J=13, 5Hz), 4.57 (1H, ddd, J=11, 8, 5Hz), 4.70 (1H, d, J=11Hz), 4.78 (1H, d, J=11Hz), 7.25 (2x1H, d, J=6Hz), 7.30-7.45 (6H, m), 7.87 (1H, d, J=5Hz), 8.33 (1H, d, J=8Hz), 8.38 (2x1H, d, J=6Hz), 11.0 (1H, s)

HPLC : 8.3 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=540

Example 16-3)

$[\alpha]_D^{25}$ = -55.2° (c 0.20, 1N-HClaq.)

mp : 212-215°C

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz), 0.81 (1H, m), 1.02 (9H, s), 1.20 (1H, m), 1.36 (1H, m), 2.25 (1H, m), 2.43 (1H, m), 2.57 (3H, d, J=5Hz), 2.65 (1H, m), 2.75-2.90 (2H, m), 2.97 (1H, dd, J=14, 5Hz), 4.55 (1H, m), 4.69 (1H, d, J=11Hz), 4.79 (1H, d, J=11Hz), 7.09 (1H, m), 7.24 (2x1H, d, J=6Hz), 7.28-7.41 (5H, m), 7.87 (1H, d, J=5Hz), 8.33 (1H, d, J=8Hz), 8.37 (2x1H, d, J=6Hz), 8.40 (1H, d, J=8Hz), 11.00 (1H, s)

HPLC : 5.4 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 35:65, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=540

Example 16-4)

$[\alpha]_D^{25}$ = -10.9° (c 0.22, 1N-HClaq.)

mp : 223-241°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.73-0.87 (1H, m), 0.78 (3H, d, J=7Hz), 1.13 (3H, t, J=7Hz), 1.19-1.42 (2H, m), 2.14 (1H, ddd, J=9, 9, 4Hz), 2.43 (1H, m), 2.45-2.60 (1H, m), 2.56 (3H, d, J=4.5Hz), 2.70 (1H, m), 2.81 (1H, dd, J=14, 11Hz), 2.94 (1H, dd, J=14, 5Hz), 3.92 (2H, q, J=7Hz), 4.55 (1H, ddd, J=11, 8, 5Hz), 4.70 (1H, d, J=11Hz), 4.76 (1H, d, J=11Hz), 6.67 (1H, dd, J=5, 5Hz), 7.25 (2x1H, d, J=7Hz), 7.30-7.42 (5H, m), 7.85 (1H, q, J=4.5Hz), 8.33 (1H, d, J=8Hz), 8.39 (2x1H, d, J=7Hz), 10.96 (1H, s)

HPLC : 7.8 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=542

Example 16-5)

$[\alpha]_D^{24}$ = -50.7° (c 0.12, 1N-HClaq.)

mp : 216-220°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz), 0.81 (1H, m), 1.24 (1H, m), 1.37 (1H, m), 2.21 (1H, m), 2.39-2.60 (2H, m), 2.55 (3H, d, J=4.5Hz), 2.83 (1H, dd, J=14, 10Hz), 2.97 (1H, dd, J=14, 5Hz), 3.05 (1H, m), 3.20 (1H, dd, J=10, 4Hz), 3.47 (1H, dd, J=10, 10Hz), 4.53-4.67 (2H, m), 4.71 (1H, d, J=11Hz), 4.79 (1H, d, J=11Hz), 5.16 (2H, s), 7.22 (2x1H, d, J=6Hz), 7.25-7.47 (11H, m), 7.90

(1H, q, J=4.5Hz), 8.03 (1H, dd, J=6, 5Hz), 8.34 (1H, d, J=8Hz), 8.37 (2x1H, d, J=6Hz), 11.17 (1H, s)

HPLC : 7.1 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:H_2O:TFA = 30:70:0.05, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=715

<u>Example 16-6)</u>

$[\alpha]_D^{25}$ = -40.7° (c 0.20, 1N-HClaq.)

mp : 228-231°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz), 0.80 (1H, m), 1.17 (3H, t, J=7Hz), 1.24 (1H, m), 1.37 (1H, m), 2.20 (1H, ddd, J=9, 9, 4Hz), 2.42 (1H, m), 2.56 (3H, d, J=5Hz), 2.71 (1H, m), 2.77-2.90 (1H, m), 2.83 (1H, dd, J=14, 11Hz), 2.95 (1H, dd, J=14, 6Hz), 3.10 (1H, d, J=14Hz), 3.16 (1H, d, J=14Hz), 4.05 (2H, q, J=7Hz), 4.57 (1H, ddd, J=11, 8, 5Hz), 4.72 (1H, d, J=11Hz), 4.80 (1H, d, J=11Hz), 7.23 (2x1H, d, J=7Hz), 7.30-7.42 (5H, m), 7.80-7.90 (2H, m), 8.32 (1H, d, J=8Hz), 8.39 (2x1H, d, J=6Hz), 11.06 (1H, s)

HPLC : 4.6 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=584

<u>Example 16-7)</u>

$[\alpha]_D^{25}$ = -22.4° (c 0.21, 1N-HClaq.)

mp : 247-250°C (dec.)

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.75 (3H, d, J=7Hz), 0.80 (1H, m), 1.22 (1H, m), 1.36 (1H, m), 2.20 (1H, ddd, J=9, 9, 4Hz), 2.37 (1H, m), 2.55 (3H, d, J=4.5Hz), 2.69-2.91 (2H, m), 2.96 (1H, dd, J=14, 6Hz), 3.62 (1H, dqq, J=7.5, 7, 7Hz), 4.54

(1H, m), 4.74 (1H, d, J=11Hz), 4.80 (1H, d, J=11Hz), 5.46 (1H, dd, J=6, 6Hz), 5.66 (1H, d, J=7.5Hz), 7.24 (2H, d, J=6Hz), 7.30-7.43 (5H, m), 7.84 (1H, q, J=4.5Hz), 8.27 (1H, d, J=8Hz), 8.41 (2H, d, J=6Hz), 11.10 (1H, s)

HPLC : 9.0 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS ..: M+H=555

Example 16-8)

$[\alpha]_D^{23}$ = -20.2° (c 0.23, 1N-HClaq.)

mp : 236-238°C (dec.)

NMR (DMSO-d_6, δ) : 0.68 (3H, d, J=7Hz), 0.74 (3H, d, J=7Hz), 0.80 (1H, m), 0.95 (3H, t, J=7.5Hz), 1.19 (1H, m), 1.35 (1H, ddd, J=12, 11, 3Hz), 2.20 (1H, ddd, J=11, 10, 3Hz), 2.37 (1H, m), 2.55 (3H, d, J=4.5Hz), 2.67-2.90 (3H, m), 2.91-3.02 (3H, m), 4.53 (1H, m), 4.73 (1H, d, J=11Hz), 4.80 (1H, d, J=11Hz), 5.53 (1H, dd, J=6, 5Hz), 5.74 (1H, t, J=6Hz), 7.23 (2x1H, d, J=6Hz), 7.29-7.42 (5H, m), 7.83 (1H, q, J=4.5Hz), 8.25 (1H, d, J=8Hz), 8.40 (2x1H, d, J=6Hz), 11.09 (1H, s)

HPLC : 6.4 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=541

Example 16-9)

$[\alpha]_D^{23}$ = -49.9° (c 0.25, 1N-HClaq.)

mp : 222-226°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz), 0.80 (1H, m), 1.16-1.55 (8H, m), 2.06-2.53 (10H, m), 2.57 (3H, d, J=4.5Hz), 2.65 (1H, m), 2.77 (1H, m), 2.83 (1H, dd, J=14, 10Hz), 2.96 (1H, dd,

J=14, 4Hz), 4.57 (1H, ddd, J=11, 8, 4Hz), 4.73 (1H, d, J=11Hz), 4.79 (1H, d, J=11Hz), 7.24 (2x1H, d, J=6Hz), 7.28-7.43 (5H, m), 7.74 (1H, dd, J=5, 5Hz), 7.86 (1H, q, J=4.5Hz), 8.31 (1H, d, J=8Hz), 8.39 (2x1H, d, J=6Hz), 11.03 (1H, s)

HPLC : 4.3 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=609

Example 16-10)

$[\alpha]_D^{23}$ = -20.7° (c 0.23, 1N-HClaq.)

mp : 215-219°C (dec.)

NMR (DMSO-d_6, δ) : 0.69 (3H, d, J=7Hz), 0.75 (3H, d, J=7Hz), 0.80 (1H, m), 1.11-1.26 (1H, m), 1.20 (9H, s), 1.36 (1H, m), 2.17 (1H, m), 2.36 (1H, m), 2.57 (3H, d, J=5Hz), 2.68 (1H, m), 2.80-2.92 (1H, m), 2.86 (1H, dd, J=14, 10Hz), 2.98 (1H, dd, J=14, 6Hz), 4.55 (1H, ddd, J=10, 8, 6Hz), 4.66 (1H, d, J=12Hz), 4.71 (1H, d, J=12Hz), 5.44 (1H, dd, J=6, 6Hz), 5.66 (1H, s), 7.24 (2H, d, J=7Hz), 7.30-7.43 (5H, m), 7.82 (1H, q, J=5Hz), 8.26 (1H, d, J=8Hz), 8.41 (2H, d, J=7Hz), 11.10 (1H, s)

HPLC : 5.7 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=569

Example 16-11)

$[\alpha]_D^{24}$ = -38.3° (c 0.12, 1N-HClaq.)

mp : 237-243°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.80 (1H, m), 1.25 (1H, m), 1.36 (1H, m), 2.06 (3H, s), 2.20 (1H, m), 2.44 (1H, m), 2.56 (3H, d, J=5Hz), 2.68-2.90 (3H, m), 2.96 (1H, dd, J=14,

6Hz), 4.33 (1H, d, J=14Hz), 4.38 (1H, d, J=14Hz), 4.56 (1H, ddd, J=10, 8, 6Hz), 4.71 (1H, d, J=11Hz), 4.80 (1H, d, J=11Hz), 7.24 (2H, d, J=6Hz), 7.30-7.41 (5H, m), 7.76 (1H, dd, J=6, 6Hz), 7.86 (1H, q, J=5Hz), 8.34 (1H, d, J=8Hz), 8.39 (2H, d, J=6Hz), 11.05 (1H, s)

HPLC : 6.9 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=570

Example 16-12)

$[\alpha]_D^{23}$ = -9.8° (c 0.21, 1N-HClaq.)

mp : 228-233°C (dec.)

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=7Hz), 0.79 (3H, d, J=7Hz), 0.80 (1H, m), 1.26 (1H, m), 1.33 (1H, m), 2.15 (1H, m), 2.43 (1H, m), 2.45 (3H, d, J=4.5Hz), 2.62-2.89 (3H, m), 2.95 (1H, dd, J=14, 4Hz), 3.47 (3H, s), 4.56 (1H, ddd, J=10, 8, 4Hz), 4.70 (1H, d, J=12Hz), 4.77 (1H, d, J=12Hz), 6.77 (1H, dd, J=5, 5Hz), 7.26 (2x1H, d, J=6Hz), 7.29-7.44 (5H, m), 7.87 (1H, q, J=4.5Hz), 8.34 (1H, d, J=8Hz), 8.39 (2x1H, d, J=6Hz), 10.98 (1H, s)

HPLC : 6.0 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=528

Example 16-13)

$[\alpha]_D^{23}$ = -38.7° (c 0.21, 1N-HClaq.)

mp : 233-236°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.79 (3H, d, J=7Hz), 0.80 (1H, m), 1.25 (1H, m), 1.34 (1H, m), 2.21 (1H, ddd, J=9, 9, 3Hz), 2.45 (1H, m), 2.56 (3H, d, J=4.5Hz), 2.65 (1H, ddd, J=13, 5, 5Hz),

2.82 (1H, dd, J=14, 10Hz), 2.85 (1H, m), 2.95 (1H, dd, J=14, 5Hz), 3.27 (3H, s), 3.70 (2H, s), 4.55 (1H, ddd, J=10, 8, 5Hz), 4.71 (1H, d, J=11Hz), 4.77 (1H, d, J=11Hz), 7.25 (2x1H, d, J=6Hz), 7.27 (1H, dd, J=5, 5Hz), 7.31-7.40 (5H, m), 7.85 (1H, q, J=4.5Hz), 8.38 (2x1H, d, J=6Hz), 8.39 (1H, d, J=8Hz), 11.05 (1H, s)

HPLC : 5.9 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=542

Example 16-14)

$[\alpha]_D^{23}$ = -18.4° (c 0.23, 1N-HClaq.)

mp : 239-243°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.82 (1H, m), 1.28 (1H, m), 1.35 (1H, m), 2.17 (1H, ddd, J=10, 9, 3Hz), 2.37-2.52 (2H, m), 2.56 (3H, d, J=4.5Hz), 2.67 (3H, s), 2.79-2.94 (1H, m), 2.84 (1H, dd, J=14, 10Hz), 2.93 (1H, dd, J=14, 5Hz), 4.51 (1H, ddd, J=10, 8, 5Hz), 4.77 (1H, d, J=11Hz), 4.81 (1H, d, J=11Hz), 6.84 (1H, dd, J=6, 6Hz), 7.27 (2x1H, d, J=7Hz), 7.31-7.44 (5H, m), 7.87 (1H, q, J=4.5Hz), 8.34 (1H, d, J=8Hz), 8.45 (2x1H, d, J=7Hz), 11.11 (1H, s)

HPLC : 5.1 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=548

Example 16-15)

$[\alpha]_D^{24}$ = -15.2° (c 0.17, 1N-HClaq.)

mp : 212-214°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.82 (1H, m), 1.26 (1H, m), 1.37 (1H, m),

2.24 (1H, m), 2.41 (1H, m), 2.57 (3H, d, J=4.5Hz), 2.77 (2H, m), 2.85 (1H, dd, J=14, 11Hz), 2.97 (1H, dd, J=14, 6Hz), 4.58 (1H, ddd, J=11, 8, 6Hz), 4.73 (1H, d, J=11Hz), 4.80 (1H, d, J=11Hz), 6.17 (1H, t, J=6Hz), 7.23-7.40 (9H, m), 7.87 (1H, q, J=4.5Hz), 8.29 (2x1H, br d, J=5Hz), 8.34 (1H, d, J=8Hz), 8.41 (2x1H, d, J=6Hz), 8.90 (1H, s), 11.18 (1H, s)

HPLC : 6.9 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=590

Example 16-16)

$[\alpha]_D^{24}$ = -6.3° (c 0.13, 1N-HClaq.)

mp : 227-229°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.73 (3H, d, J=7Hz), 0.84 (1H, m), 1.25 (1H, m), 1.38 (1H, m), 2.31 (1H, m), 2.42 (1H, m), 2.44-2.55 (1H, m), 2.47 (3H, d, J=4.5Hz), 2.62 (1H, dd, J=14, 8Hz), 2.74 (1H, dd, J=14, 7Hz), 2.87 (1H, m), 4.42 (1H, ddd, J=8, 8, 7Hz), 4.79 (1H, d, J=11Hz), 4.83 (1H, d, J=11Hz), 7.07 (2x1H, d, J=6Hz), 7.31-7.47 (5H, m), 7.50-7.63 (4H, m), 7.68-7.77 (2H, m), 7.80 (1H, q, J=4.5Hz), 8.26-8.40 (3H, m), 11.17 (1H, s)

HPLC : 6.4 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=610

Example 16-17)

$[\alpha]_D^{24}$ = -30.6° (c 0.21, 1N-HClaq.)

mp : 232-238°C (dec.)

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.73-0.86 (1H, m), 0.78 (3H, d, J=7Hz), 1.25 (1H, m), 1.32 (1H, m), 2.19 (1H, m), 2.40-2.58 (2H, m), 2.56 (3H, d,

J=4.5Hz), 2.82 (1H, dd, J=14, 12Hz), 2.88-3.02 (2H, m), 3.35-3.63 (4H, m), 3.90-4.00 (2H, m), 4.36 (1H, m), 4.52-4.68 (4H, m), 4.73 (1H, d, J=11Hz), 4.78 (1H, d, J=11Hz), 5.35 (1H, d, J=4Hz), 7.22-7.31 (1H, m), 7.25 (2x1H, d, J=6Hz), 7.32-7.42 (5H, m), 7.85 (1H, q, J=4.5Hz), 8.35-8.43 (1H, m), 8.40 (2x1H, d, J=6Hz), 11.00 (1H, s)

HPLC : 7.4 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 20:80, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=648

Example 16-18)

$[\alpha]_D^{24}$ = -48.0° (c 0.27, AcOH)

mp : 218-220°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.82 (1H, m), 1.29 (1H, m), 1.37 (1H, m), 2.20 (1H, ddd, J=9, 9, 3Hz), 2.41-2.61 (2H, m), 2.57 (3H, d, J=4Hz), 2.70 (1H, m), 2.81 (1H, dd, J=14, 11Hz), 2.96 (1H, dd, J=14, 6Hz), 4.60 (1H, ddd, J=11, 8, 6Hz), 4.74 (1H, d, J=11Hz), 4.81 (1H, d, J=11Hz), 7.09 (2x1H, d, J=7.5Hz), 7.18 (1H, dd, J=7.5, 7.5Hz), 7.27 (2x1H, d, J=6Hz), 7.31-7.52 (8H, m), 7.88 (1H, q, J=4Hz), 8.42 (2x1H, d, J=6Hz), 11.11 (1H, s)

HPLC : 7.6 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=590

Example 16-19)

$[\alpha]_D^{24}$ = +6.8° (c 0.21, AcOH)

mp : 229-234°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.81 (3H, d, J=7Hz), 0.84 (1H, m), 1.29 (1H, m), 1.41 (1H, m),

2.34 (1H, ddd, J=11, 10, 3Hz), 2.46-2.65 (1H, m), 2.58 (3H, d, J=4.5Hz), 2.78-2.93 (2H, m), 2.99 (1H, dd, J=14, 4Hz), 3.08 (1H, m), 4.56 (1H, d, J=11Hz), 4.61 (1H, m), 4.75 (1H, d, J=11Hz), 7.02 (1H, dd, J=7.5, 7.5Hz), 7.10 (1H, s), 7.12-7.35 (8H, m), 7.43 (1H, d, J=7.5Hz), 7.59 (1H, d, J=7.5Hz), 7.87 (1H, q, J=4.5Hz), 8.12 (1H, dd, J=6, 6Hz), 8.38 (2x1H, d, J=8Hz), 8.44 (1H, d, J=8Hz), 11.00 (1H, s), 11.45 (1H, s)

HPLC : 5.1 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 35:65, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=613

Example 16-20)

$[\alpha]_D^{24}$ = -36.9° (c 0.24, AcOH)

mp : 250-256°C (dec.)

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.84 (1H, m), 1.23 (1H, m), 1.40 (1H, m), 2.32-2.54 (2H, m), 2.60 (3H, d, J=4.5Hz), 2.88 (1H, dd, J=14, 11Hz), 2.93-3.07 (3H, m), 4.50-4.67 (1H, m), 4.57 (1H, d, J=11Hz), 4.77 (1H, d, J=11Hz), 7.02-7.31 (9H, m), 7.40 (1H, dd, J=8, 8Hz), 7.65 (1H, dd, J=5, 5Hz), 7.90 (1H, q, J=4.5Hz), 8.02 (1H, d, J=1Hz), 8.14 (1H, d, J=7.5Hz), 8.30-8.48 (3H, m), 10.99 (1H, s), 11.48 (1H, d, J=1Hz)

HPLC : 4.2 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 35:65, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=613

Example 16-21)

$[\alpha]_D^{24}$ = -37.0° (c 0.23, AcOH)

mp : 238-242°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.75-0.88 (1H,

m), 0.79 (3H, d, J=7Hz), 1.25 (1H, m), 1.33 (1H, m), 2.15 (1H, m), 2.45 (1H, m), 2.48-2.62 (1H, m), 2.57 (3H, d, J=4.5Hz), 2.70 (1H, m), 2.82 (1H, dd, J=14, 11Hz), 2.95 (1H, dd, J=14, 5Hz), 3.23 (3H, s), 3.47 (2H, t, J=5Hz), 3.94-4.07 (2H, m), 4.57 (1H, ddd, J=11, 8, 5Hz), 4.70 (1H, d, J=11Hz), 4.77 (1H, d, J=11Hz), 6.80 (1H, dd, J=5, 5Hz), 7.25 (2x1H, d, J=6Hz), 7.32-7.42 (5H, m), 7.87 (1H, q, J=4.5Hz), 8.37 (1H, d, J=8Hz), 8.40 (2x1H, d, J=6Hz), 10.95 (1H, s)

HPLC : 7.7 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=572

Example 16-22)

$[\alpha]_D^{24}$ = -38.1° (c 0.23, AcOH)

mp : 256-260°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.74-0.91 (1H, m), 0.79 (3H, d, J=7Hz), 0.85 (2x3H, d, J=7Hz), 1.26 (1H, m), 1.33 (1H, m), 1.80 (1H, tqq, J=7, 7, 7Hz), 2.15 (1H, ddd, J=11, 9, 3Hz), 2.44 (1H, m), 2.46-2.60 (1H, m), 2.56 (3H, d, J=4.5Hz), 2.70 (1H, m), 2.81 (1H, dd, J=14, 11Hz), 2.93 (1H, dd, J=14, 6Hz), 3.68 (2H, d, J=7Hz), 4.56 (1H, ddd, J=11, 8, 6Hz), 4.69 (1H, d, J=11Hz), 4.77 (1H, d, J=11Hz), 6.70 (1H, dd, J=6, 6Hz), 7.25 (2x1H, d, J=7Hz), 7.30-7.41 (5H, m), 7.87 (1H, q, J=4.5Hz), 8.28 (1H, d, J=8Hz), 8.35 (1H, d, J=8Hz), 8.38 (2x1H, d, J=7Hz), 10.98 (1H, s)

HPLC : 7.6 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=570

Example 16-23)

$[\alpha]_D^{24}$ = -73.6° (c 0.25, AcOH)

mp : 253-258°C (dec.)

NMR (DMSO-d_6, δ) : 0.53-0.65 (4H, m), 0.70 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz), 0.80 (1H, m), 1.23 (1H, m), 1.36 (1H, ddd, J=13, 11, 2Hz), 1.51 (1H, m), 2.20 (1H, ddd, J=11, 9, 3Hz), 2.41 (1H, ddd, J=11, 8, 3Hz), 2.56 (3H, d, J=4.5Hz), 2.63-2.90 (2H, m), 2.83 (1H, dd, J=14, 11Hz), 2.95 (1H, dd, J=14, 5Hz), 4.55 (1H, ddd, J=11, 8, 5Hz), 4.72 (1H, d, J=11Hz), 4.80 (1H, d, J=11Hz), 7.25 (2x1H, br d, J=6Hz), 7.30-7.43 (5H, m), 7.79 (1H, dd, J=5.5, 5.5Hz), 7.85 (1H, q, J=4.5Hz), 8.32 (1H, d, J=8Hz), 8.39 (2H, br), 11.03 (1H, s)

HPLC : 6.5 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 254 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=538

Example 16-24)

$[\alpha]_D^{23}$ = -12.3° (c 0.20, 1N-HClaq.)

mp : 222-231°C (dec.)

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.74-0.87 (1H, m), 0.78 (3H, d, J=7Hz), 1.12 (2x3H, d, J=7Hz), 1.26 (1H, m), 1.33 (1H, m), 2.14 (1H, ddd, J=10, 9, 3Hz), 2.45 (1H, m), 2.47-2.61 (1H, m), 2.57 (3H, d, J=4.5Hz), 2.70 (1H, m), 2.81 (1H, dd, J=14, 10Hz), 2.94 (1H, dd, J=14, 4Hz), 4.55 (1H, ddd, J=11, 8, 4Hz), 4.62-4.78 (1H, m), 4.68 (1H, d, J=11Hz), 4.77 (1H, d, J=11Hz), 6.56 (1H, dd, J=5.5, 5.5Hz), 7.25 (2x1H, d, J=6Hz), 7.28-7.42 (5H, m), 7.86 (1H, q, J=4.5Hz), 8.36 (1H, d, J=8Hz), 8.38 (2x1H, d, J=6Hz), 10.96 (1H, s)

HPLC : 9.5 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0

ml/min., at R.T.)

MASS : M+H=556

Example 16-25)

$[\alpha]_D^{23}$ = +17.0° (c 0.21, 1N-HClaq.)

mp : 237-241°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.79 (3H, d, J=7Hz), 0.83 (1H, m), 1.26 (1H, m), 1.38 (1H, m), 2.31 (1H, ddd, J=10, 9, 3Hz), 2.48 (1H, m), 2.58 (3H, d, J=4.5Hz), 2.72-2.90 (1H, m), 2.87 (1H, dd, J=14, 11Hz), 2.94-3.10 (1H, m), 2.98 (1H, dd, J=14, 5Hz), 4.56 (1H, ddd, J=11, 8, 5Hz), 4.56 (1H, d, J=12Hz), 4.74 (1H, d, J=12Hz), 6.05 (1H, br), 6.75 (1H, br), 6.83 (1H, br), 7.20-7.35 (7H, m), 7.64 (1H, dd, J=5.5, 5.5Hz), 7.87 (1H, q, J=4.5Hz), 8.38 (2x1H, d, J=6Hz), 8.40 (1H, d, J=6Hz), 10.95 (1H, s), 11.31 (1H, br)

HPLC : 8.2 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=563

Example 16-26)

$[\alpha]_D^{23}$ = +1.5° (c 0.20, 1N-HClaq.)

mp : 224-227°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.79 (3H, d, J=7Hz), 0.83 (1H, m), 1.27 (1H, m), 1.37 (1H, m), 2.36 (1H, ddd, J=9, 9, 4Hz), 2.47-2.60 (1H, m), 2.57 (3H, d, J=4.5Hz), 2.80 (1H, m), 2.83 (1H, dd, J=14, 10Hz), 2.96 (1H, dd, J=14, 5Hz), 3.18 (1H, m), 4.57 (1H, m), 4.59 (1H, dd, J=12Hz), 4.71 (1H, d, J=12Hz), 7.21-7.31 (7H, m), 7.87 (1H, q, J=4.5Hz), 8.37 (2x1H, d, J=6Hz), 8.46 (1H, d, J=8Hz), 8.72 (1H, br), 8.87 (1H, d, J=2Hz), 9.15 (1H, s), 11.05 (1H, s)

HPLC : 6.6 min. (Nuclecsil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=576

Example 16-27)

$[\alpha]_D^{23}$ = -29.4° (c 0.20, 1N-HClaq.)

mp : 225-229°C (dec.)

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.82 (1H, m), 1.12 (3H, t, J=7.5Hz), 1.28 (1H, m), 1.36 (1H, m), 2.17 (1H, ddd, J=11, 9, 3Hz), 2.32-2.53 (2H, m), 2.57 (3H, d, J=4.5Hz), 2.72-2.93 (2H, m), 2.92 (1H, dd, J=14, 5Hz), 4.50 (1H, m), 4.78 (1H, d, J=11Hz), 4.82 (1H, d, J=11Hz), 6.85 (1H, dd, J=6, 5Hz), 7.27 (2x1H, d, J=6Hz), 7.31-7.44 (5H, m), 7.88 (1H, q, J=4.5Hz), 8.34 (1H, d, J=8Hz), 8.45 (2x1H, d, J=6Hz), 11.10 (1H, s)

HPLC : 6.2 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=562

Example 16-28)

$[\alpha]_D^{23}$ = -1.3° (c 0.26, 1N-HClaq.)

mp : 225-231°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.74-0.90 (1H, m), 0.78 (3H, d, J=7Hz), 1.26 (1H, m), 1.38 (1H, m), 2.31 (1H, ddd, J=10, 9, 3Hz), 2.45 (1H, m), 2.57 (3H, d, J=4.5Hz), 2.71-3.05 (3H, m), 2.98 (1H, dd, J=14, 5Hz), 4.52-4.64 (1H, m), 4.58 (1H, d, J=12Hz), 4.74 (1H, d, J=12Hz), 6.83 (1H, s), 7.20-7.37 (7H, m), 7.70 (1H, s), 7.87 (1H, q, J=4.5Hz), 7.95 (1H, dd, J=5.5, 5.5Hz), 8.13 (1H, s), 8.31-8.46 (3H, m), 11.00 (1H, s)

HPLC : 9.8 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=564

Example 16-29)

$[\alpha]_D^{23}$ = +26.8° (c 0.23, 1N-HClaq.)

mp : 236-241°C (dec.)

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=7Hz), 0.75-0.90 (1H, m), 0.80 (3H, d, J=7Hz), 1.26 (1H, m), 1.37 (1H, m), 2.32 (1H, ddd, J=10, 9, 3Hz), 2.42-2.55 (1H, m), 2.59 (3H, d, J=4.5Hz), 2.72 (1H, ddd, J=13, 5.5, 5Hz), 2.84 (1H, dd, J=14, 11Hz), 2.91-3.06 (1H, m), 2.96 (1H, dd, J=14, 5Hz), 4.57 (1H, d, J=11Hz), 4.58 (1H, ddd, J=11, 8, 5Hz), 4.73 (1H, d, J=11Hz), 6.60 (1H, dd, J=3, 2Hz), 7.08 (1H, d, J=3Hz), 7.22-7.37 (7H, m), 7.81 (1H, d, J=2Hz), 7.88 (1H, q, J=4.5Hz), 7.96 (1H, dd, J=5.5, 5.5Hz), 8.38 (2x1H, d, J=7Hz), 8.42 (1H, d, J=8Hz), 11.00 (1H, s)

HPLC : 8.7 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=564

Example 16-30)

$[\alpha]_D^{25}$ = -35.8° (c 0.22, 1N-HClaq.)

mp : 250-257°C (dec.)

NMR (DMSO-d_6, δ) : 0.67-0.88 (1H, m), 0.73 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 1.27 (1H, m), 1.37 (1H, m), 2.22 (1H, ddd, J=10, 10, 4Hz), 2.36-2.52 (2H, m), 2.58 (3H, d, J=4.5Hz), 2.89 (1H, dd, J=14, 11Hz), 3.04 (1H, dd, J=14, 5Hz), 4.65 (1H, ddd, J=11, 8, 5Hz), 4.66 (1H, d, J=11Hz), 4.76 (1H, d, J=11Hz), 7.35 (5x1H, s), 7.46 (2x1H, d, J=6Hz),

7.91 (1H, q, J=4.5Hz), 8.45 (1H, d, J=8Hz), 8.49 (2x1H, br d, J=6Hz), 9.20 (1H, dd, J=5.5, 5.5Hz), 11.16 (1H, s)

HPLC : 10.9 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=566

Example 16-31)

$[\alpha]_D^{25}$ = -69.3° (c 0.28, 1N-HClaq.)

mp : 258-265°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.74-0.89 (1H, m), 0.78 (3H, d, J=7Hz), 1.25 (1H, m), 1.37 (1H, m), 1.85-2.28 (5H, m), 2.45 (1H, m), 2.54-2.81 (2H, m), 2.57 (3H, d, J=4.5Hz), 2.84 (1H, dd, J=14, 11Hz), 2.97 (1H, dd, J=14, 5Hz), 3.91 (1H, m), 4.59 (1H, m), 4.72 (1H, d, J=11Hz), 4.79 (1H, d, J=11Hz), 7.26 (2x1H, d, J=6Hz), 7.30-7.43 (5H, m), 7.70-7.80 (2H, m), 7.92 (1H, q, J=4.5Hz), 8.32-8.46 (3H, m), 11.11 (1H, s)

HPLC : 4.2 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=581

Example 16-32)

$[\alpha]_D^{23}$ = -1.5° (c 0.08, 1N-HClaq.)

mp : 222-229°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.74-0.86 (1H, m), 0.78 (3H, d, J=7Hz), 1.25 (1H, m), 1.33 (1H, m), 2.13 (3H, ddd, J=9, 8Hz), 2.43 (1H, m), 2.45-2.60 (1H, m), 2.56 (3H, d, J=5Hz), 2.67 (1H, m), 2.81 (1H, dd, J=14, 10Hz), 2.95 (1H, dd, J=14, 4Hz), 3.21 (2H, m), 3.91 (2H, m), 4.57 (1H, ddd, J=10, 8, 4Hz), 4.70 (1H, d, J=11Hz), 4.77 (1H, d,

J=11Hz), 5.01 (2H, s), 6.74 (1H, dd, J=5, 5Hz), 7.24 (2x1H, d, J=6Hz), 7.27-7.41 (11H, m), 7.86 (1H, q, J=5Hz), 8.35 (1H, d, J=8Hz), 8.39 (2x1H, d, J=6Hz), 10.90 (1H, s)

HPLC : 6.2 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 35:65, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=691

Example 16-33)

$[\alpha]_D^{23}$ = -44.1° (c 0.28, 1N-HClaq.)

mp : 199-205°C (dec.)

NMR (DMSO-d_6, δ) : 0.69 (3H, d, J=7Hz), 0.75 (3H, d, J=7Hz), 0.80 (1H, m), 1.21 (1H, m), 1.35 (1H, m), 1.88 (1H, m), 2.21 (1H, ddd, J=9, 9, 4Hz), 2.35-2.60 (2H, m), 2.55 (3H, d, J=4.5Hz), 2.66-2.90 (2H, m), 2.96 (1H, dd, J=14, 5Hz), 3.30 (2H, s), 4.55 (1H, m), 4.64 (1H, d, J=11Hz), 4.75 (1H, d, J=11Hz), 6.87 (1H, br), 7.22 (2x1H, d, J=6Hz), 7.35 (5x1H, s), 7.50 (1H, s), 7.72 (1H, dd, J=6, 6Hz), 7.86 (1H, q, J=4.5Hz), 8.32-8.45 (3H, m), 11.21 (1H, br)

HPLC : 5.9 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 20:80, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=578

Example 16-34)

$[\alpha]_D^{23}$ = -44.4° (c 0.10, 1N-HClaq.)

mp : 263-270°C (dec.)

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.72-0.86 (1H, m), 0.76 (3H, d, J=7Hz), 1.22 (1H, m), 1.35 (1H, m), 2.12-2.48 (6H, m), 2.53-2.70 (1H, m), 2.57 (3H, d, J=4.5Hz), 2.73-2.88 (2H, m), 2.96 (1H, dd, J=14, 6Hz), 4.57 (1H, m), 4.71 (1H, d, J=11Hz), 4.80 (1H,

d, J=11Hz), 7.24 (2x1H, d, J=6Hz), 7.28-7.42 (5H, m), 7.60 (1H, dd, J=6, 6Hz), 7.85 (1H, q, J=4.5Hz), 8.31 (1H, d, J=8Hz), 8.38 (2x1H, d, J=6Hz), 10.98 (1H, s)

HPLC : 5.0 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=570

Example 16-35)

$[\alpha]_D^{23}$ = -43.2° (c 0.22, 1N-HClaq.)

mp : 251-267°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.80 (1H, m), 1.23 (1H, m), 1.45 (1H, m), 1.84 (3H, s), 2.18 (1H, m), 2.45 (1H, m), 2.55 (3H, d, J=4.5Hz), 2.71-2.90 (3H, m), 2.96 (1H, dd, J=14, 6Hz), 3.60 (2H, d, J=5Hz), 4.55 (1H, m), 4.72 (1H, d, J=11Hz), 4.80 (1H, d, J=11Hz), 7.23 (2x1H, d, J=6Hz), 7.30-7.43 (5H, m), 7.55 (1H, t, J=5Hz), 7.85 (1H, q, J=4.5Hz), 8.02 (1H, t, J=5Hz), 8.31 (1H, d, J=8Hz), 8.40 (2x1H, d, J=6Hz), 11.02 (1H, s)

HPLC : 4.8 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=569

Example 16-36)

$[\alpha]_D^{23}$ = -36.7° (c 0.23, 1N-HClaq.)

mp : 250-253°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.74-0.88 (1H, m), 0.78 (3H, d, J=7Hz), 1.18-1.42 (2H, m), 2.21 (1H, ddd, J=10, 9, 4Hz), 2.47 (1H, m), 2.56 (3H, d, J=4.5Hz), 2.63 (1H, ddd, J=13, 5, 4Hz), 2.82 (1H, dd, J=14, 11Hz), 2.84-3.01 (1H, m), 2.95 (1H, dd,

J=14, 5Hz), 3.46 (1H, m), 3.58 (1H, m), 3.83 (1H, m), 4.55 (1H, m), 4.71-4.90 (1H, m), 4.72 (1H, d, J=11Hz), 4.78 (1H, d, J=11Hz), 5.51 (1H, d, J=5Hz), 7.21-7.30 (1H, m), 7.25 (2x1H, d, J=6Hz), 7.32-7.42 (5H, m), 7.86 (1H, q, J=4.5Hz), 8.35-8.43 (1H, m), 8.39 (2x1H, d, J=6Hz), 11.06 (1H, s)

HPLC : 4.5 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=558

Example 16-37)

$[\alpha]_D^{23}$ = -21.9° (c 0.23, 1N-HClaq.)

mp : 214-221°C (dec.)

NMR (DMSO-d_6, δ) : 0.69 (3H, d, J=7Hz), 0.75 (3H, d, J=7Hz), 0.81 (1H, m), 1.20 (1H, m), 1.36 (1H, m), 2.21 (1H, ddd, J=9, 9, 4Hz), 2.38 (1H, m), 2.55 (3H, d, J=4.5Hz), 2.70-2.91 (3H, m), 2.96 (1H, dd, J=14, 6Hz), 3.61 (3H, s), 3.73-3.80 (2H, m), 4.54 (1H, m), 4.75 (1H, d, J=11Hz), 4.80 (1H, d, J=11Hz), 5.97 (1H, dd, J=6, 6Hz), 6.21 (1H, dd, J=6, 6Hz), 7.23 (2x1H, d, J=7Hz), 7.31-7.43 (5H, m), 7.83 (1H, q, J=4.5Hz), 8.26 (1H, d, J=8Hz), 8.41 (2x1H, d, J=7Hz), 11.09 (1H, s)

HPLC : 5.9 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=585

Example 16-38)

$[\alpha]_D^{23}$ = -15.9° (c 0.20, 1N-HClaq.)

mp : 238-242°C (dec.)

NMR (DMSO-d_6, δ) : 0.68 (3H, d, J=7Hz), 0.74 (3H, d, J=7Hz), 0.80 (1H, m), 1.20 (1H, m), 1.34 (1H, m), 2.20 (1H, ddd, J=9, 9, 4Hz), 2.37 (1H, m), 2.51

(3H, d, J=4.5Hz), 2.56 (3H, d, J=4.5Hz), 2.68-2.83 (2H, m), 2.85 (1H, dd, J=14, 10Hz), 2.97 (1H, dd, J=14, 6Hz), 4.53 (1H, ddd, J=10, 8, 6Hz), 4.74 (1H, d, J=11Hz), 4.79 (1H, d, J=11Hz), 5.61 (1H, dd, J=6, 6Hz), 5.66 (1H, q, J=4.5Hz), 7.24 (2x1H, d, J=6Hz), 7.31-7.42 (5H, m), 7.85 (1H, q, J=4.5Hz), 8.27 (1H, d, J=8Hz), 8.41 (2x1H, d, J=6Hz), 11.06 (1H, s)

HPLC : 5.0 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=527

Example 16-39)

$[\alpha]_D^{23}$ = -56.2° (c 0.22, 1N-HClaq.)

mp : 243-247°C (dec.)

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.76 (3H, d, J=7Hz), 0.80 (1H, m), 1.22 (1H, m), 1.34 (1H, m), 2.20 (1H, ddd, J=9, 9, 4Hz), 2.47 (1H, m), 2.55 (3H, d, J=4.5Hz), 2.69 (1H, m), 2.80-2.96 (1H, m), 2.83 (1H, dd, J=14, 11Hz), 2.96 (1H, dd, J=14, 5Hz), 3.45-3.63 (2H, m), 3.84 (1H, m), 4.53 (1H, ddd, J=11, 8, 5Hz), 4.72 (1H, d, J=11Hz), 4.79 (1H, d, J=11Hz), 4.89 (1H, br), 5.48 (1H, d, J=6Hz), 7.23 (2x1H, d, J=6Hz), 7.30-7.40 (6H, m), 7.84 (1H, q, J=4.5Hz), 8.33 (1H, d, J=8Hz), 8.39 (2x1H, d, J=6Hz), 11.10 (1H, s)

HPLC : 10.0 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 20:80, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=558

Example 16-40)

$[\alpha]_D^{23}$ = -45.3° (c 0.20, 1N-HClaq.)

mp : 254-259°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=6.5Hz), 0.74-0.90 (1H, m), 0.78 (3H, d, J=6.5Hz), 1.25 (1H, m), 1.38 (1H, m), 2.19 (1H, m), 2.41 (1H, m), 2.57 (3H, d, J=4.5Hz), 2.66-2.97 (3H, m), 2.95 (1H, dd, J=14, 6Hz), 3.11 (3H, s), 3.97 (2H, s), 4.60 (1H, m), 4.74 (1H, d, J=11Hz), 4.80 (1H, d, J=11Hz), 7.25 (2x1H, d, J=6Hz), 7.31-7.42 (5H, m), 7.91 (1H, q, J=4.5Hz), 8.14 (1H, dd, J=6, 6Hz), 8.36 (1H, d, J=8Hz), 8.40 (2x1H, d, J=6Hz), 11.12 (1H, s)

HPLC : 6.4 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M-H=588

Example 16-41)

$[\alpha]_D^{23}$ = -11.2° (c 0.21, 1N-HClaq.)

mp : 236-239°C (dec.)

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.73-0.89 (1H, m), 0.78 (3H, d, J=7Hz), 1.26 (1H, m), 1.33 (1H, m), 1.98 (3H, s), 2.14 (1H, m), 2.35-2.60 (2H, m), 2.56 (3H, d, J=4.5Hz), 2.69 (1H, m), 2.81 (1H, dd, J=13, 11Hz), 2.94 (1H, dd, J=13, 5Hz), 4.03-4.20 (4H, m), 4.56 (1H, ddd, J=11, 8, 5Hz), 4.69 (1H, d, J=11Hz), 4.76 (1H, d, J=11Hz), 6.88 (1H, dd, J=5, 5Hz), 7.25 (2x1H, d, J=6Hz), 7.30-7.42 (5H, m), 7.87 (1H, q, J=4.5Hz), 8.35 (1H, d, J=8Hz), 8.39 (2x1H, d, J=6Hz), 10.96 (1H, s)

HPLC : 9.3 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=600

Example 16-42)

$[\alpha]_D^{25}$ = -55.4° (c 0.23, AcOH)

mp : 231-234°C (dec.)

NMR ($DMSO-d_6$, δ) : 0.70 (3H, d, J=7Hz), 0.73-0.86 (1H, m), 0.78 (3H, d, J=7Hz), 1.22 (1H, m), 1.28-1.42 (1H, m), 1.33 (3x3H, s), 2.42-2.60 (2H, m), 2.57 (3H, d, J=4.5Hz), 2.75 (1H, m), 2.80 (1H, dd, J=14, 10Hz), 2.97 (1H, dd, J=14, 5Hz), 3.54 (2H, dd, J=6, 6Hz), 3.97 (1H, dt, J=8, 6Hz), 4.62 (1H, m), 4.66 (1H, d, J=11Hz), 4.77 (1H, d, J=11Hz), 5.00 (1H, t, J=6Hz), 6.54 (1H, d, J=8Hz), 7.26 (2x1H, d, J=6Hz), 7.31-7.40 (5H, m), 7.59 (1H, dd, J=6, 6Hz), 7.90 (1H, q, J=4.5Hz), 8.33-8.41 (1H, m), 8.37 (2x1H, d, J=6Hz), 11.03 (1H, s)

HPLC : 5.6 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 30:70, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=657

Example 16-43)

$[\alpha]_D^{24}$ = -41.3° (c 0.20, 1N-HClaq.)

mp : 241-245°C (dec.)

NMR ($DMSO-d_6$, δ) : 0.71 (3H, d, J=7Hz), 0.74-0.85 (1H, m), 0.78 (3H, d, J=7Hz), 1.25 (1H, m), 1.36 (1H, m), 2.08-2.23 (2H, m), 2.30-2.54 (5H, m), 2.59 (3H, d, J=5Hz), 2.70 (1H, m), 2.80 (1H, dd, J=14, 11Hz), 2.96 (1H, dd, J=14, 5Hz), 4.60 (1H, m), 4.70 (1H, d, J=11Hz), 4.73-4.82 (1H, m), 4.78 (1H, d, J=11Hz), 7.26 (2x1H, d, J=6Hz), 7.31-7.40 (5H, m), 7.83-7.93 (2H, m), 8.31-8.42 (1H, m), 8.36 (2x1H, d, J=6Hz), 11.09 (1H, s)

HPLC : 6.8 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:H_2O:TFA = 25:75:0.05, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=582

Example 16-44)

$[\alpha]_D^{24}$ = -52.8° (c 0.20, 1N-HClaq.)

mp : 250-256°C (dec.)

NMR ($DMSO-d_6$, δ) : 0.72 (3H, d, J=7Hz), 0.74-0.88 (1H, m), 0.79 (3H, d, J=7Hz), 1.27 (1H, m), 1.36 (1H, m), 2.02-2.25 (2H, m), 2.26-2.54 (5H, m), 2.57 (3H, d, J=5Hz), 2.63 (2H, m), 2.81 (1H, dd, J=13, 11Hz), 2.96 (1H, dd, J=13, 5Hz), 4.60 (1H, m), 4.70-4.83 (1H, m), 4.71 (1H, d, J=11Hz), 4.78 (1H, d, J=11Hz), 7.27 (2x1H, d, J=6Hz), 7.30-7.42 (5H, m), 7.83-7.98 (2H, m), 8.30-8.46 (3H, m), 11.09 (1H, s)

HPLC : 6.4 min. (Nucleosil 5C18, 4 mmφ x 15 cm, $MeCN:H_2O:TFA$= 25:75:0.05, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=582

Example 16-45)

$[\alpha]_D^{24}$ = -40.0° (c 0.19, 1N-HClaq.)

mp : 223-227°C (dec.)

NMR ($DMSO-d_6$, δ) : 0.71 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.81 (1H, m), 1.25 (1H, m), 1.30-1.46 (1H, m), 1.36 (3x3H, s), 2.19 (1H, m), 2.45 (1H, m), 2.56 (3H, d, J=4.5Hz), 2.70-2.90 (3H, m), 2.97 (1H, dd, J=14, 5Hz), 3.45 (1H, dd, J=15, 5Hz), 3.51 (1H, dd, J=15, 5Hz), 4.56 (1H, m), 4.72 (1H, d, J=11Hz), 4.80 (1H, d, J=11Hz), 6.81 (1H, dd, J=5, 5Hz), 7.24 (2x1H, d, J=6Hz), 7.28-7.42 (5H, m), 7.50 (1H, dd, J=5, 5Hz), 7.86 (1H, q, J=4.5Hz), 8.32 (1H, d, J=8Hz), 8.40 (2x1H, d, J=6Hz), 11.03 (1H, s)

HPLC : 4.1 min. (Nucleosil 5C18, 4 mmφ x 15 cm, $MeCN:H_2O:TFA$ = 35:65:0.05, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=627

Example 16-46)

$[\alpha]_D^{24}$ = -10.5° (c 0.22, 1N-HClaq.)

mp : 259-263°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.74-0.88 (1H, m), 0.78 (3H, d, J=7Hz), 1.27 (1H, m), 1.33 (1H, m), 2.23 (1H, ddd, J=9, 9, 4Hz), 2.45-2.60 (2H, m), 2.56 (3H, d, J=4.5Hz), 2.82 (1H, dd, J=14, 11Hz), 2.93 (1H, dd, J=14, 6Hz), 3.02 (1H, m), 4.55 (1H, ddd, J=11, 8, 6Hz), 4.66 (1H, d, J=11Hz), 4.74 (1H, d, J=11Hz), 7.25 (2x1H, d, J=6Hz), 7.30-7.39 (5H, m), 7.80 (1H, br), 7.86 (1H, q, J=4.5Hz), 8.01-8.10 (2H, m), 8.28 (2x1H, d, J=6Hz), 8.35 (1H, d, J=8Hz), 11.02 (1H, s)

HPLC : 5.6 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:H_2O:TFA = 25:75:0.05, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=541

Example 16-47)

$[\alpha]_D^{23}$ = -17.2° (c 0.21, 1N-HClaq.)

mp : 234-238°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.83 (1H, m), 1.21-1.42 (2H, m), 2.17 (1H, ddd, J=9, 9, 3Hz), 2.35-2.47 (2H, m), 2.56 (3H, d, J=4.5Hz), 2.72 (3H, s), 2.77-3.00 (3H, m), 4.48 (1H, m), 4.77 (1H, d, J=11Hz), 4.81 (1H, d, J=11Hz), 6.83 (1H, dd, J=6, 6Hz), 7.25-7.45 (5H, m), 7.30 (1H, dd, J=7.5, 5Hz), 7.67 (1H, br d, J=7.5Hz), 7.87 (1H, q, J=4.5Hz), 8.33 (1H, d, J=8Hz), 8.39 (1H, br d, J=5Hz), 8.48 (1H, s), 11.10 (1H, s)

HPLC : 5.7 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:H_2O:TFA = 25:75:0.05, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=548

Example 16-48)

$[\alpha]_D^{24}$ = -36.9° (c 0.22, 1N-HClaq.)

mp : 228-230°C (dec.)

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.74-0.85 (1H, m), 0.78 (3H, d, J=7Hz), 1.25 (1H, m), 1.35 (1H, m), 2.05 (3H, s), 2.16 (1H, m), 2.41 (1H, m), 2.46-2.61 (1H, m), 2.55 (3H, d, J=4.5Hz), 2.71 (1H, m), 2.81 (1H, dd, J=14, 11Hz), 2.95 (1H, dd, J=14, 5Hz), 4.30 (1H, d, J=15Hz), 4.37 (1H, d, J=15Hz), 4.51 (1H, m), 4.70 (1H, d, J=11Hz), 4.79 (1H, d, J=11Hz), 7.19 (1H, dd, J=7.5, 5Hz), 7.28-7.41 (5H, m), 7.63 (1H, br d, J=7.5Hz), 7.73 (1H, dd, J=5, 5Hz), 7.84 (1H, q, J=4.5Hz), 8.28-8.36 (2H, m), 8.43 (1H, s), 11.03 (1H, s)

HPLC : 6.0 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:H_2O:TFA = 25:75:0.05, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=570

Example 16-49)

$[\alpha]_D^{24}$ = -11.5° (c 0.22, 1N-HClaq.)

mp : 230-234°C (dec.)

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.73-0.86 (1H, m), 0.78 (3H, d, J=7Hz), 1.13 (3H, t, J=7Hz), 1.20-1.40 (2H, m), 2.13 (1H, ddd, J=9, 9, 4Hz), 2.43 (1H, m), 2.45-2.59 (1H, m), 2.55 (3H, d, J=5Hz), 2.65 (1H, m), 2.80 (1H, dd, J=14, 11Hz), 2.93 (1H, dd, J=14, 5Hz), 3.92 (2H, q, J=7Hz), 4.52 (1H, m), 4.70 (1H, d, J=11Hz), 4.76 (1H, d, J=11Hz), 6.69 (1H, dd, J=5, 5Hz), 7.21 (1H, dd, J=7.5, 5Hz), 7.31-7.41 (5H, m), 7.65 (1H, br d, J=7.5Hz), 7.85 (1H, q, J=5Hz), 8.28-8.37 (2H, m), 8.44 (1H, br s), 10.96 (1H, s)

HPLC : 8.1 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:H_2O:TFA = 25:75:0.05, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=542

The following compounds were obtained in substantially the same manner as that of Example 12-5).

Example 17-1)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-isobutyrylaminomethylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{25}$ = -32.9° (c 0.19, 1N-HClaq.)

mp : 249-252°C (dec.)

NMR ($DMSO-d_6$, δ) : 0.71 (3H, d, J=7Hz), 0.76 (3H, d, J=7Hz), 0.85 (1H, m), 0.93 (3H, d, J=7Hz), 0.94 (3H, d, J=7Hz), 1.22 (1H, m), 1.38 (1H, m), 2.14-2.32 (2H, m), 2.40 (1H, m), 2.55 (3H, d, J=4Hz), 2.60-2.89 (3H, m), 2.96 (1H, dd, J=14, 5Hz), 4.55 (1H, m), 7.19-7.32 (3H, m), 7.85 (1H, q, J=4Hz), 8.30 (1H, d, J=8Hz), 8.36 (2x1H, d, J=6Hz), 8.70 (1H, s), 10.29 (1H, s)

HPLC : 5.1 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=450

Example 17-2)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-pivaloylaminomethylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -30.0° (c 0.21, 1N-HClaq.)

mp : 226-229°C (dec.)

NMR ($DMSO-d_6$, δ) : 0.71 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz), 0.86 (1H, m), 1.04 (9H, s), 1.22 (1H, m), 1.37 (1H, m), 2.28 (1H, ddd, J=11, 10, 3Hz), 2.44 (1H, m), 2.53-2.65 (1H, m), 2.56 (3H, d, J=5Hz), 2.82-2.98 (1H, m), 2.84 (1H, dd, J=14, 11Hz), 2.96 (1H, dd, J=14, 5Hz), 4.54 (1H, ddd, J=11, 8, 5Hz), 6.87 (1H, dd, J=5.5, 5.5Hz), 7.24 (2x1H, d, J=6Hz), 7.86 (1H, q, J=5Hz), 8.36 (1H, d, J=8Hz), 8.37 (2x1H, d, J=6Hz), 8.73 (1H, s), 10.29 (1H, s)

HPLC : 6.8 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M-H=462

Example 17-3)

N-[(2R,3R)-3-Ethoxycarbonylaminomethyl-4-hydroxyamino-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -23.5° (c 0.24, 1N-HClaq.)

mp : 232-237°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.86 (1H, m), 1.14 (3H, t, J=7Hz), 1.27 (1H, m), 1.38 (1H, m), 2.17 (1H, ddd, J=11, 9, 3Hz), 2.42 (1H, m), 2.44-2.60 (1H, m), 2.56 (3H, d, J=5Hz), 2.76 (1H, m), 2.81 (1H, dd, J=13, 10Hz), 2.95 (1H, dd, J=13, 5Hz), 3.92 (2H, q, J=7Hz), 4.55 (1H, ddd, J=10, 8, 5Hz), 6.50 (1H, dd, J=5, 4Hz), 7.25 (2H, d, J=7Hz), 7.85 (1H, q, J=5Hz), 8.32 (1H, d, J=8Hz), 8.40 (2H, d, J=7Hz), 8.76 (1H, s), 10.32 (1H, s)

HPLC : 5.5 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=452

Example 17-4)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-methylcarbamoyl-acetamidomethylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -27.1° (c 0.25, 1N-HClaq.)

mp : 225-231°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz), 0.86 (1H, m), 1.22 (1H, m), 1.38 (1H, m), 2.21 (1H, m), 2.44 (1H, m), 2.56 (3H, d, J=5Hz), 2.60 (3H, d, J=4Hz), 2.70-2.81 (2H, m), 2.83 (1H, dd, J=14, 11Hz), 2.96 (1H, dd, J=14, 5Hz), 2.97

(2H, s), 4.55 (1H, m), 7.23 (2x1H, d, J=7Hz), 7.77 (1H, dd, J=5, 5Hz), 7.84-7.99 (2H, m), 8.34-8.43 (2H, m), 8.38 (2x1H, d, J=7Hz)

HPLC : 4.1 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=479

Example 17-5)

N-[(2R,3R)-3-Ethoxycarbonylacetamidomethyl-4-hydroxyamino-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -31.8° (c 0.21, 1N-HClaq.)

mp : 226-232°C (dec.)

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz), 0.87 (1H, m), 1.20 (3H, t, J=7Hz), 1.24 (1H, m), 1.40 (1H, m), 2.22 (1H, m), 2.42 (1H, m), 2.56 (3H, d, J=5Hz), 2.74-2.90 (3H, m), 2.96 (1H, dd, J=14, 5Hz), 3.13 (1H, d, J=15Hz), 3.18 (1H, d, J=15Hz), 4.07 (2H, q, J=7Hz), 4.56 (1H, m), 7.19-7.31 (2H, br), 7.72 (1H, dd, J=6, 6Hz), 7.85 (1H, q, J=5Hz), 8.25-8.48 (2H, br), 8.30 (1H, d, J=8Hz), 8.77 (1H, s), 10.38 (1H, s)

HPLC : 6.3 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=494

Example 17-6)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-(3-isopropylureidomethyl)succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{25}$ = -25.4° (c 0.21, 1N-HClaq.)

mp : 222-227°C (dec.)

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.75 (3H, d, J=7Hz), 0.88 (1H, m), 1.00 (2x3H, d, J=7Hz), 1.20

(1H, m), 1.39 (1H, m), 2.37 (1H, m), 2.57 (3H, d, J=5Hz), 2.75-2.84 (2H, m), 2.86 (1H, dd, J=14, 10Hz), 2.97 (1H, dd, J=14, 6Hz), 3.62 (1H, dqq, J=7, 7, 7Hz), 4.54 (1H, ddd, J=10, 8, 6Hz), 5.35 (1H, dd, J=6, 6Hz), 5.72 (1H, d, J=7Hz), 7.25 (2x1H, br d, J=6Hz), 7.30-7.43 (5H, m), 7.84 (1H, q, J=5Hz), 8.25 (1H, d, J=8Hz), 8.42 (2x1H, br d, J=6Hz), 8.80 (1H, s), 10.46 (1H, s)

HPLC : 5.9 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=465

Example 17-7)

N-[(2R,3R)-3-(3-Ethylureidomethyl)-4-hydroxyamino-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -25.3° (c 0.25, 1N-HClaq.)

mp : 237-243°C (dec.)

NMR (DMSO-d_6, δ) : 0.69 (3H, d, J=7Hz), 0.75 (3H, d, J=7Hz), 0.87 (1H, m), 0.96 (3H, t, J=7Hz), 1.20 (1H, m), 1.38 (1H, m), 2.20 (1H, m), 2.37 (1H, m), 2.55 (3H, d, J=4.5Hz), 2.70-3.04 (6H, m), 4.53 (1H, m), 5.44 (1H, t, J=6Hz), 5.80 (1H, t, J=5Hz), 7.25 (2x1H, d, J=6Hz), 7.85 (1H, q, J=4.5Hz), 8.25 (1H, d, J=8Hz), 8.41 (2x1H, d, J=6Hz), 8.80 (1H, s), 10.45 (1H, s)

HPLC : 4.6 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=451

Example 17-8)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-[3-(piperidin-1-yl)propionylaminomethyl]succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -26.3° (c 0.20, 1N-HClaq.)

mp : 227-232°C (dec.)

NMR ($DMSO-d_6$, δ) : 0.72 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz), 0.87 (1H, m), 1.24 (1H, m), 1.30-1.58 (7H, m), 2.10-2.25 (3H, m), 2.27-2.54 (7H, m), 2.57 (3H, d, J=5Hz), 2.72 (2H, t, J=6Hz), 2.83 (1H, dd, J=13, 10Hz), 2.96 (1H, dd, J=13, 4Hz), 4.55 (1H, ddd, J=10, 8, 4Hz), 7.24 (2x1H, d, J=6Hz), 7.68 (1H, dd, J=6, 5Hz), 7.86 (1H, q, J=5Hz), 8.29 (1H, d, J=8Hz), 8.38 (2x1H, d, J=6Hz), 8.74 (1H, br), 10.34 (1H, s)

HPLC : 4.4 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=519

Example 17-9)

N-[(2R,3R)-3-(3-tert-Butylureidomethyl)-4-hydroxyamino-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -27.2° (c 0.22, 1N-HClaq.)

mp : 196-200°C (dec.)

NMR ($DMSO-d_6$, δ) : 0.71 (3H, d, J=7Hz), 0.75 (3H, d, J=7Hz), 0.88 (1H, m), 1.19 (1H, m), 1.20 (9H, s), 1.40 (1H, m), 2.17 (1H, m), 2.35 (1H, m), 2.57 (3H, d, J=5Hz), 2.73 (1H, m), 2.80-2.93 (2H, m), 2.98 (1H, dd, J=14, 4Hz), 4.54 (1H, m), 5.35 (1H, dd, J=5, 5Hz), 5.72 (1H, s), 7.25 (2x1H, d, J=6Hz), 7.83 (1H, q, J=5Hz), 8.26 (1H, d, J=8Hz), 8.42 (2x1H, d, J=6Hz), 8.82 (1H, br), 10.46 (1H, s)

HPLC : 5.7 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=479

Example 17-10)

N-[(2R,3R)-3-Acetoxyacetamidomethyl-4-hydroxyamino-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{24}$ = -26.4° (c 0.25, 1N-HClaq.)

mp : 230-236°C (dec.)

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz), 0.87 (1H, ddd, J=12, 9, 3Hz), 1.24 (1H, m), 1.39 (1H, ddd, J=12, 9, 3Hz), 2.08 (3H, s), 2.22 (1H, ddd, J=10, 10, 3Hz), 2.43 (1H, ddd, J=11, 11, 3Hz), 2.56 (3H, d, J=4.5Hz), 2.71 (1H, ddd, J=14, 5, 4Hz), 2.84 (1H, dd, J=14, 11Hz), 2.89 (1H, m), 2.97 (1H, dd, J=14, 6Hz), 4.35 (1H, d, J=12Hz), 4.40 (1H, d, J=12Hz), 4.55 (1H, ddd, J=11, 8, 6Hz), 7.25 (2x1H, d, J=6Hz), 7.58 (1H, dd, J=6, 5Hz), 7.86 (1H, q, J=4.5Hz), 8.32 (1H, d, J=8Hz), 8.40 (2x1H, d, J=6Hz), 8.80 (1H, s), 10.39 (1H, s)

HPLC : 4.6 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=548

Example 17-11)

N-[(2R,3R)-3-Carboxylacetamidomethyl-4-hydroxyamino-2-iosbutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -32.6° (c 0.22, 1N-HClaq.)

mp : 234-239°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.76 (3H, d, J=7Hz), 0.87 (1H, m), 1.23 (1H, m), 1.40 (1H, m), 2.21 (1H, m), 2.43 (1H, m), 2.55 (3H, d, J=4.5Hz), 2.75-2.90 (3H, m), 2.96 (1H, dd, J=14, 6Hz), 3.06 (1H, d, J=15Hz), 3.11 (1H, d, J=15Hz), 4.56 (1H, m), 7.25 (2x1H, d, J=6Hz), 7.71 (1H, dd, J=5.5, 5.5Hz), 7.86 (1H, q, J=4.5Hz), 8.30 (1H, d, J=8Hz), 8.40 (2x1H, d, J=6Hz), 8.78 (1H, br), 10.37 (1H, s)

HPLC : 3.7 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0

ml/min., at R.T.)

MASS : M+H=466

Example 17-12)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-(methoxycarbonylaminomethyl)succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -27.1° (c 0.21, 1N-HClaq.)

mp : 226-230°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.87 (1H, m), 1.27 (1H, m), 1.38 (1H, m), 2.17 (1H, m), 2.31 (1H, m), 2.57 (3H, d, J=4.5Hz), 2.68-2.89 (3H, m), 2.95 (1H, dd, J=14, 4Hz), 3.47 (3H, s), 4.56 (1H, m), 6.57 (1H, dd, J=5, 5Hz), 7.26 (2x1H, d, J=6Hz), 7.85 (1H, q, J=4.5Hz), 8.31 (1H, d, J=8Hz), 8.40 (2x1H, d, J=6Hz), 8.75 (1H, s), 10.32 (1H, s)

HPLC : 4.2 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=438

Example 17-13)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-(methoxyacetamidomethyl)succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -20.4° (c 0.35, 1N-HClaq.)

mp : 241-244°C (dec.)

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.87 (1H, m), 1.26 (1H, m), 1.38 (1H, m), 2.24 (1H, ddd, J=10, 10, 3Hz), 2.45 (1H, m), 2.57 (3H, d, J=4.5Hz), 2.62 (1H, ddd, J=12, 5, 4Hz), 2.83 (1H, dd, J=14, 11Hz), 2.90-3.05 (3H, m), 3.28 (3H, s), 3.71 (2H, s), 4.54 (1H, ddd, J=11, 8, 5Hz), 7.10 (1H, dd, J=5, 5Hz), 7.25 (2x1H, d, J=6Hz), 7.85 (1H, q, J=4.5Hz), 8.36 (1H, d, J=8Hz), 8.39 (2x1H, d, J=6Hz), 8.81 (1H, s), 10.40 (1H, s)

HPLC : 4.1 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=452

Example 17-14)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-(mesylamino-methyl)succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{21}$ = -15.8° (c 0.35, 1N-HClaq.)

mp : 223-226°C (dec.)

NMR (DMSO-d_6, δ) : 0.75 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.90 (1H, m), 1.31 (1H, m), 1.40 (1H, m), 2.19 (1H, m), 2.35-2.48 (2H, m), 2.57 (3H, d, J=4.5Hz), 2.68 (3H, s), 2.80-2.95 (1H, m), 2.85 (1H, dd, J=14, 11Hz), 2.94 (1H, dd, J=14, 5Hz), 4.51 (1H, ddd, J=11, 7.5, 5Hz), 6.72 (1H, dd, J=7, 5Hz), 7.29 (2x1H, d, J=7Hz), 7.88 (1H, q, J=4.5Hz), 8.33 (1H, d, J=7.5Hz), 8.46 (2x1H, d, J=6Hz), 8.83 (1H, s), 10.46 (1H, s)

HPLC : 3.8 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=458

Example 17-15)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-[3-(4-pyridyl)-ureidomethyl]succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{24}$ = -44.6° (c 0.27, 1N-HClaq.)

mp : 223-229°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.79 (3H, d, J=7Hz), 0.90 (1H, m), 1.28 (1H, m), 1.41 (1H, m), 2.24 (1H, ddd, J=10, 9, 3Hz), 2.42 (1H, ddd, J=10, 10, 3Hz), 2.57 (3H, d, J=4.5Hz), 2.68-2.91 (2H, m), 2.76 (1H, dd, J=14, 10Hz), 2.96 (1H, dd, J=14, 5Hz), 4.57 (1H, ddd, J=10, 8, 5Hz), 6.10 (1H, dd,

J=6, 6Hz), 7.26 (2x1H, d, J=6Hz), 7.37 (2x1H, br d, J=5Hz), 7.87 (1H, q, J=4.5Hz), 8.21-8.36 (2H, m), 8.33 (1H, d, J=8Hz), 8.40 (2x1H, d, J=6Hz), 8.87 (1H, br), 9.00 (1H, s), 10.45 (1H, s)

HPLC : 4.1 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=500

Example 17-16)

N-[(2R,3R)-3-Benzenesulfonylaminomethyl-4-hydroxyamino-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{24}$ = -19.9° (c 0.13, 1N-HClaq.)

mp : 233-237°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.75 (3H, d, J=7Hz), 0.90 (1H, m), 1.26 (1H, m), 1.42 (1H, m), 2.25-2.51 (3H, m), 2.47 (3H, d, J=4.5Hz), 2.56 (1H, dd, J=14, 7Hz), 2.71 (1H, dd, J=14, 7Hz), 2.86 (1H, m), 4.40 (1H, ddd, J=8, 7, 7Hz), 7.04 (2x1H, d, J=6Hz), 7.46 (1H, dd, J=7, 5Hz), 7.49-7.58 (3H, m), 7.70 (1H, d, J=5Hz), 7.72 (1H, d, J=5Hz), 7.79 (1H, q, J=4.5Hz), 8.28 (1H, d, J=8Hz), 8.35 (2x1H, d, J=6Hz), 8.87 (1H, s), 10.49 (1H, s)

HPLC : 6.1 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 15:85, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=520

Example 17-17)

N-[(2R,3R)-3-Glycoloylaminomethyl-4-hydroxyamino-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{22}$ = -20.0° (c 0.38, 1N-HClaq.)

mp : 221-226°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.88 (1H, m), 1.26 (1H, m), 1.38 (1H, m),

2.24 (1H, ddd, J=9, 9, 4Hz), 2.41-2.53 (1H, m), 2.55 (3H, d, J=4.5Hz), 2.71 (1H, ddd, J=13, 5, 4Hz), 2.85 (1H, dd, J=14, 10Hz), 2.91-3.08 (1H, m), 2.96 (1H, dd, J=14, 5Hz), 3.75 (2H, br), 4.54 (1H, ddd, J=10, 8, 5Hz), 5.46 (1H, br), 7.11 (1H, dd, J=6, 5Hz), 7.26 (2x1H, d, J=6Hz), 7.85 (1H, q, J=4.5Hz), 8.41 (2x1H, d, J=6Hz), 8.85 (1H, s), 10.47 (1H, s)

HPLC : 3.6 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=438

Example 17-18)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-(phenoxycarbonylaminomethyl)succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{22}$ = -34.5° (c 0.30, 1N-HClaq.)

mp : 222-226°C (dec.)

NMR (DMSO-d_6, δ) : 0.75 (3H, d, J=7Hz), 0.81 (3H, d, J=7Hz), 0.89 (1H, m), 1.29 (1H, m), 1.40 (1H, m), 2.22 (1H, ddd, J=10, 9, 3Hz), 2.36-2.53 (2H, m), 2.57 (3H, d, J=4.5Hz), 2.80 (1H, m), 2.82 (1H, dd, J=14, 11Hz), 2.95 (1H, dd, J=14, 4Hz), 4.60 (1H, ddd, J=11, 8, 4Hz), 7.11 (2x1H, d, J=7.5Hz), 7.19 (1H, dd, J=7.5, 7.5Hz), 7.22-7.32 (3H, m), 7.38 (2x1H, dd, J=7.5, 7.5Hz), 7.87 (1H, q, J=4.5Hz), 8.35 (1H, d, J=8Hz), 8.42 (2x1H, br), 8.82 (1H, s), 10.42 (1H, s)

HPLC : 3.6 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 20:80, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=500

Example 17-19)

N-[(2R,3R)-4-Hydroxyamino-3-(2-indolylcarbonylamino-

methyl)-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{22}$ = -24.3° (c 0.30, 1N-HClaq.)

mp : 234-238°C (dec.)

NMR (DMSO-d_6, δ) : 0.75 (3H, d, J=7Hz), 0.82 (3H, d, J=7Hz), 0.92 (1H, ddd, J=13, 10, 3Hz), 1.30 (1H, m), 1.45 (1H, m), 2.39 (1H, ddd, J=10, 9, 3Hz), 2.46-2.65 (1H, m), 2.59 (3H, d, J=4.5Hz), 2.80 (1H, ddd, J=11, 4, 3Hz), 2.87 (1H, dd, J=14, 10Hz), 2.98 (1H, dd, J=14, 6Hz), 3.15 (1H, m), 4.59 (1H, ddd, J=10, 8, 6Hz), 7.02 (1H, dd, J=7.5, 7.5Hz), 7.05 (1H, s), 7.17 (1H, dd, J=7.5, 7.5Hz), 7.22-7.35 (2H, br), 7.42 (1H, d, J=7.5Hz), 7.60 (1H, d, J=7.5Hz), 7.89 (1H, q, J=4.5Hz), 7.95 (1H, dd, J=4, 4Hz), 8.29-8.50 (2H, br), 8.43 (1H, d, J=8Hz), 8.75 (1H, s), 10.37 (1H, s), 11.48 (1H, s)

HPLC : 6.3 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 20:80, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=523

Example 17-20)

N-[(2R,3R)-4-Hydroxyamino-3-(3-indolylcarbonylamino-methyl)-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{22}$ = -25.4° (c 0.25, 1N-HClaq.)

mp : 218-222°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.92 (1H, m), 1.22 (1H, m), 1.44 (1H, m), 2.36-2.53 (2H, m), 2.59 (3H, d, J=4.5Hz), 2.88 (1H, dd, J=14, 10Hz), 2.90-3.15 (3H, m), 4.58 (1H, m), 7.08 (1H, dd, J=7.5, 7.5Hz), 7.14 (1H, dd, J=7.5, 7.5Hz), 7.26 (2x1H, d, J=6Hz), 7.41 (1H, d, J=7.5Hz), 7.90 (1H, q, J=4.5Hz), 7.96 (1H, d, J=2Hz), 8.11 (1H, d, J=7.5Hz), 8.32-8.45 (3H, m), 8.75 (1H, s), 10.38 (1H, s), 11.49 (1H, d, J=2Hz)

HPLC : 3.7 min. (Nucleosil 5C18, 4 mmϕ x 15 cm,

MeCN:0.05% TFAaq. = 20:80, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=523

Example 17-21)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-(2-methoxyethoxycarbonylaminomethyl)succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{22}$ = -19.5° (c 0.30, 1N-HClaq.)

mp : 223-227°C (dec.)

NMR ($DMSO-d_6$, δ) : 0.72 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.86 (1H, m), 1.26 (1H, m), 1.38 (1H, m), 2.17 (1H, ddd, J=10, 10, 3Hz), 2.43 (1H, m), 2.46-2.60 (1H, m), 2.56 (3H, d, J=4.5Hz), 2.76 (1H, m), 2.81 (1H, dd, J=14, 11Hz), 2.93 (1H, dd, J=14, 5Hz), 3.25 (3H, s), 3.47 (2H, t, J=4Hz), 4.00 (2H, t, J=4Hz), 4.55 (1H, ddd, J=11, 8, 5Hz), 6.63 (1H, dd, J=5.5, 5.5Hz), 7.25 (2x1H, d, J=6Hz), 7.86 (1H, q, J=4.5Hz), 8.33 (1H, d, J=8Hz), 8.39 (2x1H, d, J=6Hz), 8.76 (1H, s), 10.30 (1H, s)

HPLC : 5.7 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 254 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=482

Example 17-22)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-(isobutoxycarbonylaminomethyl)succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{22}$ = -25.4° (c 0.31, 1N-HClaq.)

mp : 232-236°C (dec.)

NMR ($DMSO-d_6$, δ) : 0.73 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.82-0.93 (1H, m), 0.88 (2x3H, d, J=7Hz), 1.26 (1H, m), 1.38 (1H, m), 1.82 (1H, tqq, J=7, 7, 7Hz), 2.18 (1H, m), 2.33 (1H, m), 2.36-2.61 (1H, m), 2.56 (3H, d, J=4.5Hz), 2.77 (1H, m), 2.82 (1H, dd, J=14, 10Hz), 2.94 (1H, dd, J=14, 6Hz), 3.68

(2H, d, J=7Hz), 4.55 (1H, ddd, J=10, 8, 6Hz), 6.50 (1H, dd, J=6, 6Hz), 7.26 (2x1H, d, J=5Hz), 7.87 (1H, q, J=4.5Hz), 8.33 (1H, d, J=8Hz), 8.39 (2x1H, d, J=5Hz), 10.31 (1H, s)

HPLC : 5.8 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 15:85, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=480

Example 17-23)

N-[(2R,3R)-3-Cyclopropanecarbonylaminomethyl-4-hydroxyamino-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{22}$ = -37.9° (c 0.29, 1N-HClaq.)

mp : 236-241°C (dec.)

NMR (DMSO-d_6, δ) : 0.52-0.66 (4H, m), 0.70 (3H, d, J=7Hz), 0.75 (3H, d, J=7Hz), 0.85 (1H, m), 1.20 (1H, m), 1.38 (1H, m), 1.48 (1H, m), 2.20 (1H, ddd, J=11, 7, 7Hz), 2.39 (1H, ddd, J=11, 9, 3Hz), 2.54 (3H, d, J=4.5Hz), 2.70-2.82 (2H, m), 2.84 (1H, dd, J=14, 11Hz), 2.95 (1H, dd, J=14, 5Hz), 4.54 (1H, ddd, J=11, 8, 5Hz), 7.22 (2H, br), 7.65 (1H, dd, J=5.5, 5.5Hz), 7.84 (1H, q, J=4.5Hz), 8.28 (1H, d, J=8Hz), 8.37 (2H, br), 8.76 (1H, s), 10.36 (1H, s)

HPLC : 4.6 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=448

Example 17-24)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-(isopropoxycarbonylaminomethyl)succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{25}$ = -27.1° (c 0.32, 1N-HClaq.)

mp : 230-236°C (dec.)

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.86 (1H, m), 1.14 (2x3H, d, J=7Hz), 1.25

(1H, m), 1.37 (1H, m), 2.17 (1H, ddd, J=9, 9, 4Hz), 2.42 (1H, m), 2.44-2.59 (1H, m), 2.56 (3H, d, J=4.5Hz), 2.75 (1H, m), 2.81 (1H, dd, J=14, 10Hz), 2.93 (1H, dd, J=14, 5Hz), 4.54 (1H, ddd, J=10, 8, 5Hz), 4.69 (1H, qq, J=7, 7Hz), 6.37 (1H, dd, J=5, 5Hz), 7.25 (2x1H, d, J=6Hz), 7.84 (1H, q, J=4.5Hz), 8.32 (1H, d, J=8Hz), 8.40 (2x1H, br d, J=6Hz), 8.75 (1H, s), 10.29 (1H, s)

HPLC : 7.9 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=466

Example 17-25)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-(2-pyrrolylcarbonylaminomethyl)succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -23.0° (c 0.21, 1N-HClaq.)

mp : 220-224°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.88 (1H, m), 1.25 (1H, m), 1.40 (1H, m), 2.33 (1H, ddd, J=10, 9, 4Hz), 2.38-2.50 (1H, m), 2.56 (3H, d, J=4.5Hz), 2.77 (1H, m), 2.85 (1H, dd, J=14, 11Hz), 2.95 (1H, dd, J=14, 4Hz), 3.08 (1H, m), 4.55 (1H, m), 6.03 (1H, dd, J=3, 3Hz), 6.67 (1H, br), 6.81 (1H, br), 7.24 (2x1H, d, J=6Hz), 7.44 (1H, dd, J=5.5, 5.5Hz), 7.87 (1H, q, J=4.5Hz), 8.30-8.43 (3H, m), 8.73 (1H, s), 10.32 (1H, s), 11.32 (1H, br)

HPLC : 8.5 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=473

Example 17-26)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-(pyrazin-2-yl-

carbonylaminomethyl)succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -22.8° (c 0.25, 1N-HClaq.)

mp : 234-238°C (dec.)

NMR (DMSO-d_6, δ) : 0.74 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.90 (1H, ddd, J=13, 10, 3Hz), 1.29 (1H, m), 1.42 (1H, m), 2.39 (1H, ddd, J=10, 9, 4Hz), 2.48-2.62 (1H, m), 2.57 (3H, d, J=4.5Hz), 2.76-2.91 (2H, m), 2.96 (1H, dd, J=14, 5Hz), 3.26 (1H, m), 4.57 (1H, m), 7.26 (2x1H, d, J=7Hz), 7.87 (1H, q, J=4.5Hz), 8.25 (1H, dd, J=5.5, 5.5Hz), 8.37 (2x1H, d, J=7Hz), 8.44 (1H, d, J=8Hz), 8.73 (1H, br), 8.83 (1H, s), 8.88 (1H, d, J=2Hz), 9.17 (1H, s), 10.46 (1H, s)

HPLC : 6.0 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=486

Example 17-27)

N-[(2R,3R)-3-Ethanesulfonylaminomethyl-4-hydroxyamino-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -22.3° (c 0.24, 1N-HClaq.)

mp : 240-246°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.79 (3H, d, J=7Hz), 0.89 (1H, ddd, J=13, 10, 3Hz), 1.10 (3H, t, J=7.5Hz), 1.30 (1H, m), 1.40 (1H, m), 2.18 (1H, ddd, J=13, 10, 3Hz), 2.32-2.47 (2H, m), 2.57 (3H, d, J=4.5Hz), 2.70 (2H, q, J=7.5Hz), 2.79-2.98 (3H, m), 4.50 (1H, m), 6.73 (1H, dd, J=6, 5Hz), 7.27 (2x1H, d, J=6Hz), 7.88 (1H, q, J=4.5Hz), 8.31 (1H, d, J=8Hz), 8.45 (2x1H, br d, J=6Hz), 8.81 (1H, s), 10.44 (1H, s)

HPLC : 4.5 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=472

Example 17-28)

N-[(2R,3R)-3-(3-Furoylaminomethyl)-4-hydroxyamino-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -25.0° (c 0.28, 1N-HClaq.)

mp : 225-228°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.79 (3H, d, J=7Hz), 0.89 (1H, ddd, J=13, 11, 2.5Hz), 1.27 (1H, m), 1.41 (1H, ddd, J=13, 11, 2.5Hz), 2.34 (1H, ddd, J=10, 10, 4Hz), 2.45 (1H, m), 2.57 (3H, d, J=4.5Hz), 2.73 (1H, ddd, J=13, 5.5, 4Hz), 2.86 (1H, dd, J=14, 10Hz), 2.92-3.08 (1H, m), 2.98 (1H, dd, J=14, 4Hz), 4.57 (1H, m), 6.80 (1H, s), 7.28 (2x1H, d, J=6Hz), 7.69 (1H, s), 7.75 (1H, dd, J=5.5, 5.5Hz), 7.87 (1H, q, J=4.5Hz), 8.11 (1H, s), 8.30-8.47 (3H, m), 8.72 (1H, s), 10.34 (1H, s)

HPLC : 6.4 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=474

Example 17-29)

N-[(2R,3R)-3-(2-Furoylaminomethyl)-4-hydroxyamino-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -22.8° (c 0.23, 1N-HClaq.)

mp : 231-235°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.89 (1H, m), 1.27 (1H, m), 1.41 (1H, m), 2.35 (1H, ddd, J=10, 9, 4Hz), 2.43-2.55 (1H, m), 2.57 (3H, d, J=4.5Hz), 2.70 (1H, ddd, J=12, 5.5, 4Hz), 2.84 (1H, dd, J=13, 11Hz), 2.95 (1H, dd, J=13, 5Hz), 3.08 (1H, m), 4.56 (1H, ddd, J=11, 8, 5Hz), 6.60 (1H, dd, J=3, 2Hz), 7.05 (1H, d, J=3Hz), 7.25 (2x1H, d, J=6Hz), 7.73 (1H, dd, J=5.5, 5.5Hz),

7.80 (1H, d, J=2Hz), 7.87 (1H, q, J=4.5Hz), 8.36 (2x1H, d, J=6Hz), 8.40 (1H, d, J=8Hz), 8.77 (1H, s), 10.37 (1H, s)

HPLC : 7.0 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10.90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=474

Example 17-30)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-(trifluoroacetamidomethyl)succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{25}$ = -24.9° (c 0.24, 1N-HClaq.)

mp : 223-227°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.84 (1H, m), 1.28 (1H, m), 1.39 (1H, m), 2.24 (1H, ddd, J=9, 9, 3Hz), 2.30-2.52 (2H, m), 2.57 (3H, d, J=4.5Hz), 2.81 (1H, dd, J=14, 11Hz), 2.89 (1H, m), 2.96 (1H, dd, J=14, 4Hz), 4.60 (1H, m), 7.29 (2x1H, d, J=6Hz), 7.88 (1H, q, J=4.5Hz), 8.29-8.45 (3H, m), 8.78 (1H, s), 9.02 (1H, dd, J=5, 5Hz), 10.41 (1H, s)

HPLC : 5.9 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=476

Example 17-31)

N-{(2R,3R)-4-Hydroxyamino-2-isobutyl-3-[(S)-2-pyrrolidon-5-ylcarbonylaminomethyl]succinyl}-L-4-pyridylalanine methylamide

$[\alpha]_D^{22}$ = -36.5° (c 0.22, 1N-HClaq.)

mp : 248-254°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.79 (3H, d, J=7Hz), 0.87 (1H, m), 1.26 (1H, m), 1.40 (1H, m), 1.83-2.30 (5H, m), 2.40 (1H, m), 2.55-2.65 (1H, m),

2.58 (3H, d, J=4.5Hz), 2.72 (1H, m), 2.87 (1H, dd, J=14, 11Hz), 3.00 (1H, dd, J=14, 5Hz), 3.91 (1H, m), 4.59 (1H, ddd, J=11, 8, 5Hz), 7.36 (2x1H, d, J=6Hz), 7.61 (1H, dd, J=6, 6Hz), 7.68 (1H, s), 7.90 (1H, q, J=4.5Hz), 8.35 (1H, d, J=8Hz), 8.44 (2x1H, d, J=6Hz), 8.74 (1H, s), 10.38 (1H, s)

HPLC : 4.3 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=491

Example 17-32)

N-[(2R,3R)-4-Hydroxyamino-3-(imidazol-4-ylacetylamino-methyl)-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{22}$ = -28.1° (c 0.23, 1N-HClaq.)

mp : 234-242°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.76 (3H, d, J=7Hz), 0.86 (1H, m), 1.23 (1H, m), 1.38 (1H, m), 2.21 (1H, ddd, J=9, 9, 4Hz), 2.45 (1H, m), 2.55 (3H, d, J=4.5Hz), 2.67-2.90 (3H, m), 2.95 (1H, dd, J=14, 6Hz), 3.30 (2H, s), 4.53 (1H, m), 6.90 (1H, s), 7.23 (2x1H, d, J=6Hz), 7.52 (2H, dd, J=6, 6Hz), 7.63 (1H, s), 7.85 (1H, q, J=4.5Hz), 8.31-8.43 (3H, m), 10.46 (1H, s)

HPLC : 3.1 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=488

Example 17-33)

N-[(2R,3R)-3-(3-Carboxypropionylaminomethyl)-4-hydroxy-amino-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{22}$ = -32.4° (c 0.26, 1N-HClaq.)

mp : 215-221°C (dec.)

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=7Hz), 0.77 (3H, d,

J=7Hz), 0.86 (1H, m), 1.22 (1H, m), 1.38 (1H, m), 2.13-2.47 (6H, m), 2.57 (3H, d, J=4.5Hz), 2.68-2.78 (2H, m), 2.83 (1H, dd, J=14, 11Hz), 2.96 (1H, dd, J=14, 6Hz), 4.57 (1H, ddd, J=11, 8, 6Hz), 7.23 (2x1H, d, J=6Hz), 7.47 (1H, dd, J=5.5, 5.5Hz), 7.86 (1H, q, J=4.5Hz), 8.30 (1H, d, J=8Hz), 8.40 (2x1H, d, J=6Hz), 8.74 (1H, br), 10.31 (1H, s)

HPLC : 3.9 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=480

Example 17-34)

N-[(2R,3R)-3-(N-Acetylglycyl)aminomethyl-4-hydroxyamino-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{22}$ = -18.7° (c 0.37, 1N-HClaq.)

mp : 225-233°C (dec.)

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.86 (1H, m), 1.24 (1H, m), 1.39 (1H, m), 1.87 (3H, s), 2.20 (1H, m), 2.45 (1H, m), 2.54 (3H, d, J=4.5Hz), 2.73 (1H, m), 2.83-2.96 (2H, m), 2.85 (1H, dd, J=14, 10Hz), 2.96 (1H, dd, J=14, 7Hz), 3.60 (2H, d, J=6Hz), 4.53 (1H, ddd, J=10, 8, 7Hz), 7.23 (2x1H, d, J=6Hz), 7.44 (1H, dd, J=5.5, 5.5Hz), 7.84 (1H, q, J=4.5Hz), 8.09 (1H, t, J=6Hz), 8.26 (1H, d, J=8Hz), 8.40 (2x1H, d, J=6Hz), 8.79 (1H, s), 10.39 (1H, s)

HPLC : 4.3 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=479

Example 17-35)

N-{(2R,3R)-3-[(2R)-Glyceroylaminomethyl]-4-hydroxyamino-2-isobutylsuccinyl}-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -7.6° (c 0.41, 1N-HClaq.)

mp : 214-220°C (dec.)

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.87 (1H, m), 1.25 (1H, m), 1.38 (1H, m), 2.23 (1H, ddd, J=9, 9, 4Hz), 2.47 (1H, m), 2.55 (3H, d, J=4.5Hz), 2.61 (1H, ddd, J=13, 5, 4Hz), 2.83 (1H, dd, J=13, 11Hz), 2.91-3.06 (1H, m), 2.95 (1H, dd, J=13, 6Hz), 3.45 (1H, m), 3.58 (1H, m), 3.83 (1H, m), 4.54 (1H, ddd, J=11, 8, 6Hz), 4.73 (1H, dd, J=6, 6Hz), 5.50 (1H, d, J=5Hz), 7.15 (1H, dd, J=5.5, 5.5Hz), 7.24 (2x1H, d, J=6Hz), 7.84 (1H, q, J=4.5Hz), 8.33 (1H, d, J=8Hz), 8.40 (2x1H, d, J=6Hz), 8.84 (1H, s), 10.43 (1H, s)

HPLC : 4.0 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=468

Example 17-36)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-[(3-methoxycarbonylmethyl)ureidomethyl]succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{22}$ = -27.4° (c 0.31, 1N-HClaq.)

mp : 210-214°C (dec.)

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.74 (3H, d, J=7Hz), 0.87 (1H, m), 1.20 (1H, m), 1.39 (1H, m), 2.21 (1H, ddd, J=10, 9, 4Hz), 2.38 (1H, ddd, J=11, 10, 2Hz), 2.54 (3H, d, J=4.5Hz), 2.71-2.92 (3H, m), 2.97 (1H, dd, J=14, 5Hz), 3.61 (3H, s), 3.75 (2H, d, J=6Hz), 4.53 (1H, m), 5.97 (1H, dd, J=6, 6Hz), 6.26 (1H, t, J=6Hz), 7.22 (2x1H, d, J=7Hz), 7.83 (1H, q, J=4.5Hz), 8.24 (1H, d, J=8Hz), 8.40 (2x1H, d, J=7Hz), 8.81 (1H, s), 10.45 (1H, s)

HPLC : 5.2 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0

ml/min., at R.T.)

MASS : M+H=495

Example 17-37)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-(3-methylureidomethyl)succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -22.1° (c 0.36, 1N-HClaq.)

mp : 223-226°C (dec.)

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.74 (3H, d, J=7Hz), 0.87 (1H, m), 1.20 (1H, m), 1.38 (1H, m), 2.20 (1H, m), 2.38 (1H, ddd, J=10, 10, 3Hz), 2.51 (3H, d, J=4.5Hz), 2.56 (3H, d, J=4.5Hz), 2.80 (2H, t, J=6Hz), 2.86 (1H, dd, J=14, 10Hz), 2.97 (1H, dd, J=14, 6Hz), 4.53 (1H, ddd, J=10, 8, 6Hz), 5.49 (1H, t, J=6Hz), 5.71 (1H, q, J=4.5Hz), 7.23 (2x1H, d, J=6Hz), 7.85 (1H, q, J=4.5Hz), 8.28 (1H, d, J=8Hz), 8.40 (2x1H, d, J=6Hz), 8.78 (1H, s), 10.43 (1H, s)

HPLC : 4.0 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=437

Example 17-38)

N-{(2R,3R)-4-Hydroxyamino-2-isobutyl-3-[3-(methylcarbamoylmethyl)ureidomethyl]succinyl}-L-4-pyridylalanine methylamide

$[\alpha]_D^{21}$ = -26.2° (c 0.28, 1N-HClaq.)

mp : 233-237°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.75 (3H, d, J=7Hz), 0.87 (1H, m), 1.21 (1H, m), 1.38 (1H, m), 2.17 (1H, ddd, J=10, 9, 4Hz), 2.38 (1H, ddd, J=10, 10, 3Hz), 2.53-2.69 (1H, m), 2.56 (3H, d, J=4.5Hz), 2.60 (3H, d, J=4.5Hz), 2.70-2.86 (1H, m), 2.84 (1H, dd, J=14, 10Hz), 2.99 (1H, dd, J=14, 5Hz), 3.53 (1H, dd, J=17, 6Hz), 3.58 (1H, dd, J=17, 6Hz), 4.54

(1H, ddd, J=10, 8, 5Hz), 5.80 (1H, dd, J=6, 6Hz), 6.17 (1H, dd, J=6, 6Hz), 7.25 (2x1H, d, J=6Hz), 7.74 (1H, q, J=4.5Hz), 7.85 (1H, q, J=4.5Hz), 8.25 (1H, d, J=8Hz), 8.40 (2x1H, d, J=6Hz), 8.80 (1H, s), 10.43 (1H, s)

HPLC : 4.3 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=494

Example 17-39)

N-{(2R,3R)-3-[(2S)-Glyceroylaminomethyl]-4-hydroxyamino-2-isobutylsuccinyl}-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -33.2° (c 0.36, 1N-HClaq.)

mp : 211-220°C (dec.)

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=6.3Hz), 0.76 (3H, d, J=6.3Hz), 0.86 (1H, m), 1.24 (1H, m), 1.40 (1H, m), 2.23 (1H, m), 2.40-2.62 (1H, m), 2.54 (3H, d, J=4.5Hz), 2.70 (1H, m), 2.78-3.10 (3H, m), 3.46-3.66 (2H, m), 3.85 (1H, m), 4.52 (1H, m), 5.00 (1H, br), 5.48 (1H, d, J=6.2Hz), 7.23 (2x1H, d, J=5.5Hz), 7.29 (1H, m), 7.81 (1H, q, J=4.5Hz), 8.28 (1H, d, J=8.1Hz), 8.39 (2x1H, d, J=5.5Hz), 8.85 (1H, s), 10.48 (1H, s)

HPLC : 4.2 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=468

Example 17-40)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-(methanesulfonyl-acetylaminomethyl)succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -26.0° (c 0.36, 1N-HClaq.)

mp : 247-252°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.78 (3H, d,

J=7Hz), 0.87 (1H, m), 1.25 (1H, m), 1.41 (1H, m), 2.20 (1H, m), 2.41 (1H, m), 2.56 (3H, d, J=4.5Hz), 2.70-2.87 (2H, m), 2.84 (1H, dd, J=14, 12Hz), 2.96 (1H, dd, J=14, 5Hz), 3.10 (3H, s), 3.98 (2H, s), 4.58 (1H, ddd, J=12, 8, 5Hz), 7.24 (2x1H, d, J=6Hz), 7.87 (1H, q, J=4.5Hz), 8.02 (1H, dd, J=6, 6Hz), 8.28 (1H, d, J=8Hz), 8.40 (2x1H, d, J=6Hz), 8.77 (1H, s), 10.40 (1H, s)

HPLC : 4.5 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=500

Example 17-41)

N-[(2R,3R)-3-(2-Acetoxyethoxy)carbonylaminomethyl-4-hydroxyamino-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -19.8° (c 0.34, 1N-HClaq.)

mp : 223-228°C (dec.)

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.86 (1H, m), 1.27 (1H, m), 1.38 (1H, m), 2.02 (3H, s), 2.17 (1H, m), 2.35-2.61 (2H, m), 2.56 (3H, d, J=4.5Hz), 2.76 (1H, m), 2.81 (1H, dd, J=14, 11Hz), 2.94 (1H, dd, J=14, 5Hz), 4.03-4.20 (4H, m), 4.56 (1H, ddd, J=11, 8, 5Hz), 6.70 (1H, dd, J=5, 5Hz), 7.24 (2H, d, J=6Hz), 7.85 (1H, q, J=4.5Hz), 8.32 (1H, d, J=8Hz), 8.38 (2H, d, J=6Hz), 8.75 (1H, s), 10.30 (1H, s)

HPLC : 8.2 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=510

Example 17-42)

N-[(2R,3R)-4-Hydroxyamino-3-(2-hydroxyethoxy)carbonyl-

aminomethyl-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -22.4° (c 0.32, 1N-HClaq.)

mp : 215-219°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.79 (3H, d, J=7Hz), 0.87 (1H, m), 1.27 (1H, m), 1.38 (1H, m), 2.17 (1H, ddd, J=9, 9, 4Hz), 2.43 (1H, m), 2.45-2.60 (1H, m), 2.56 (3H, d, J=4.5Hz), 2.70-2.84 (1H, m), 2.82 (1H, dd, J=14, 11Hz), 2.94 (1H, dd, J=14, 5Hz), 3.53 (2H, t, J=4Hz), 3.90 (2H, t, J=4Hz), 4.56 (1H, ddd, J=11, 8, 5Hz), 4.75 (1H, br), 6.52 (1H, dd, J=5, 5Hz), 7.25 (2x1H, d, J=6Hz), 7.86 (1H, q, J=4.5Hz), 8.33 (1H, d, J=8Hz), 8.40 (2x1H, d, J=6Hz), 8.77 (1H, s), 10.31 (1H, s)

HPLC : 4.4 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=468

Example 17-43)

N-{(2R,3R)-3-[(2S)-2-tert-Butoxycarbonylamino-3-hydroxy-propionyl]aminomethyl]-4-hydroxyamino-2-isobutylsuccinyl}-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -38.1° (c 0.38, 1N-HClaq.)

mp : 214-217°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz), 0.85 (1H, m), 1.23 (1H, m), 1.31-1.47 (1H, m), 1.39 (9H, s), 2.15 (1H, m), 2.41-2.70 (2H, m), 2.56 (3H, d, J=4.5Hz), 2.70-2.84 (1H, m), 2.81 (1H, dd, J=13, 10Hz), 2.97 (1H, dd, J=13, 5Hz), 3.53 (2H, br d, J=5Hz), 3.95 (1H, dt, J=8, 5Hz), 4.60 (1H, ddd, J=10, 8, 5Hz), 6.50 (1H, d, J=8Hz), 7.26 (2x1H, d, J=6Hz), 7.52 (1H, dd, J=5, 5Hz), 7.90 (1H, q, J=4.5Hz), 8.33 (1H, d, J=8Hz), 8.39 (2x1H, d, J=6Hz), 8.79 (1H, s), 10.36 (1H, s)

HPLC : 5.1 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 15:85, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=567

Example 17-44)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-(methanesulfonylaminomethyl)succinyl]-L-3-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -19.4° (c 0.31, 1N-HClaq.)

mp : 230-233°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.90 (1H, m), 1.22-1.48 (2H, m), 2.17 (1H, m), 2.30-2.46 (2H, m), 2.55 (3H, d, J=5Hz), 2.70 (3H, s), 2.77-3.00 (3H, m), 4.47 (1H, m), 6.70 (1H, dd, J=5, 5Hz), 7.03 (1H, dd, J=7.5, 5Hz), 7.68 (1H, br d, J=7.5Hz), 7.85 (1H, q, J=5Hz), 8.30 (1H, d, J=8Hz), 8.39 (1H, br), 8.47 (1H, s), 8.82 (1H, s), 10.43 (1H, s)

HPLC : 4.3 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=458

Example 17-45)

N-[(2R,3R)-3-Acetoxyacetylaminomethyl-4-hydroxyamino-2-isobutylsuccinyl]-L-3-pyridylalanine methylamide

$[\alpha]_D^{24}$ = -26.9° (c 0.25, 1N-HClaq.)

mp : 206-208°C (dec.)

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=7Hz), 0.79 (3H, d, J=7Hz), 0.86 (1H, m), 1.25 (1H, m), 1.38 (1H, m), 2.08 (3H, s), 2.20 (1H, ddd, J=9, 9, 4Hz), 2.42 (1H, ddd, J=10, 9, 2Hz), 2.47-2.60 (1H, m), 2.55 (3H, d, J=4.5Hz), 2.75-2.90 (2H, m), 2.95 (1H, dd, J=14, 6Hz), 4.34 (1H, d, J=15Hz), 4.38 (1H, d, J=15Hz), 4.51 (1H, m), 7.20 (1H, dd, J=7.5, 5Hz),

7.56 (1H, dd, J=6, 6Hz), 7.63 (1H, br d, J=7.5Hz), 7.84 (1H, q, J=4.5Hz), 8.29 (1H, d, J=8Hz), 8.33 (1H, d, J=5Hz), 8.43 (1H, s), 8.78 (1H, s), 10.37 (1H, s)

HPLC : 5.1 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=480

Example 17-46)

N-{(2R,3R)-4-Hydroxyamino-2-isobutyl-3-[(2R)-5-oxo-tetrahydrofuran-2-ylcarbonylaminomethyl]succinyl}-L-4-pyridylalanine methylamide methanesulfonate

$[\alpha]_D^{24}$ = -13.4° (c 0.35, 1N-HClaq.)

mp : 197-204°C (dec.)

NMR (DMSO-d_6, δ) : 0.74 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.88 (1H, m), 1.27 (1H, m), 1.38 (1H, m), 2.09 (1H, m), 2.15 (1H, ddd, J=9, 9, 3Hz), 2.28-2.53 (5H, m), 2.30 (3H, s), 2.60 (3H, d, J=5Hz), 2.78 (1H, m), 3.07 (1H, dd, J=13, 11Hz), 3.22 (1H, dd, J=13, 5Hz), 4.60 (1H, m), 4.70 (1H, ddd, J=11, 8, 5Hz), 4.78 (1H, dd, J=8, 6Hz), 7.73 (1H, dd, J=6, 5Hz), 7.85-7.98 (1H, m), 7.91 (2x1H, d, J=6Hz), 8.42 (1H, d, J=8Hz), 8.75 (2x1H, d, J=6Hz), 10.46 (1H, s)

HPLC : 4.5 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=492

Example 17-47)

N-[(2R,3R)-3-Hydroxyacetylaminomethyl-4-hydroxyamino-2-isobutylsuccinyl]-L-3-pyridylalanine methylamide methanesulfonate

$[\alpha]_D^{24}$ = -17.5° (c 0.30, 1N-HClaq.)

mp : 169-171°C (dec.)

NMR (DMSO-d_6, δ) : 0.75 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.89 (1H, m), 1.28 (1H, m), 1.38 (1H, m), 2.16 (1H, ddd, J=10, 9, 4Hz), 2.32 (3H, s), 2.35-2.53 (2H, m), 2.60 (3H, d, J=5Hz), 2.85 (1H, m), 3.00 (1H, dd, J=14, 11Hz), 3.15 (1H, dd, J=14, 4Hz), 3.72 (1H, d, J=16Hz), 3.76 (1H, d, J=16Hz), 4.60 (1H, m), 7.05 (1H, dd, J=5, 5Hz), 7.85-7.96 (2H, m), 8.32-8.45 (2H, m), 8.70 (1H, d, J=5Hz), 8.78 (1H, s), 10.52 (1H, s)

HPLC : 4.0 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=438

Example 17-48)

N-{(2R,3R)-4-Hydroxyamino-2-isobutyl-3-[(2S)-5-oxotetrahydrofuran-2-ylcarbonylaminomethyl]succinyl}-L-4-pyridylalanine methylamide methanesulfonate

$[\alpha]_D^{24}$ = -27.1° (c 0.27, 1N-HClaq.)

mp : 210-214°C (dec.)

NMR (DMSO-d_6, δ) : 0.77 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.87 (1H, m), 1.27 (1H, m), 1.38 (1H, m), 2.05 (1H, m), 2.19 (1H, ddd, J=9, 9, 3Hz), 2.30-2.53 (5H, m), 2.32 (3H, s), 2.60 (3H, d, J=4.5Hz), 2.67 (1H, m), 3.07 (1H, dd, J=14, 12Hz), 3.23 (1H, dd, J=14, 5Hz), 4.71 (1H, ddd, J=12, 8, 5Hz), 4.80 (1H, dd, J=8, 6Hz), 7.82 (1H, dd, J=6, 6Hz), 7.88-7.98 (3H, m), 8.43 (1H, d, J=8Hz), 8.75 (2x1H, d, J=6Hz), 10.43 (1H, s)

HPLC : 4.7 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=492

Example 17-49)

N-[(2R,3R)-3-Ethoxycarbonylaminomethyl-4-hydroxyamino-2-isobutylsuccinyl]-L-3-pyridylalanine methylamide methanesulfonate

$[\alpha]_D^{24}$ = -23.2° (c 0.31, 1N-HClaq.)

mp : 189-191°C (dec.)

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.87 (1H, m), 1.14 (3H, t, J=7Hz), 1.25 (1H, m), 1.37 (1H, m), 2.10 (1H, ddd, J=9, 9, 3Hz), 2.22 (1H, ddd, J=12, 5, 4Hz), 2.32 (3H, s), 2.38 (1H, m), 2.59 (3H, d, J=5Hz), 2.69 (1H, m), 3.00 (1H, dd, J=14, 12Hz), 3.15 (1H, dd, J=14, 5Hz), 3.93 (2H, q, J=7Hz), 4.61 (1H, m), 6.50 (1H, dd, J=5, 5Hz), 7.81-7.92 (2H, m), 8.29-8.43 (2H, m), 8.70 (1H, d, J=5Hz), 8.78 (1H, s), 10.35 (1H, s)

HPLC : 6.1 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=452

Example 17-50)

N-[(2R,3R)-3-(N-tert-Butoxycarbonylglycyl)aminomethyl-4-hydroxyamino-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{24}$ = -22.2° (c 0.20, 1N-HClaq.)

mp : 217-219°C (dec.)

NMR (DMSO-d_6, δ) : 0.72 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz), 0.87 (1H, m), 1.13-1.48 (2H, m), 1.38 (3x3H, s), 2.20 (1H, m), 2.45 (1H, m), 2.55 (3H, d, J=4.5Hz), 2.74-2.91 (3H, m), 2.96 (1H, dd, J=14, 6Hz), 3.45 (1H, dd, J=16, 5Hz), 3.50 (1H, dd, J=16, 7Hz), 4.56 (1H, m), 6.82 (1H, dd, J=5, 5Hz), 7.24 (2x1H, d, J=6Hz), 7.87 (1H, q, J=4.5Hz), 8.28 (1H, d, J=8Hz), 8.41 (2x1H, d, J=6Hz), 8.78 (1H, s), 10.35 (1H, s)

HPLC : 8.3 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 15:85, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=537

Example 17-51)

N-[(2R,3R)-4-Hydroxyamino-2-isobutyl-3-(oxamoylamino-methyl)succinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{24}$ = -14.8° (c 0.38, 1N-HClaq.)

mp : 221-224°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.89 (1H, m), 1.28 (1H, m), 1.38 (1H, m), 2.22 (1H, ddd, J=10, 9, 4Hz), 2.32-2.52 (2H, m), 2.60 (3H, d, J=4Hz), 2.97 (1H, m), 3.05 (1H, dd, J=14, 12Hz), 3.19 (1H, dd, J=14, 5Hz), 4.67 (1H, ddd, J=12, 8, 5Hz), 7.79-8.00 (6H, m), 8.48 (1H, d, J=8Hz), 8.71 (2x1H, br d, J=6Hz), 10.46 (1H, s)

HPLC : 4.5 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=451

Example 17-52)

N-[(2R,3R)-3-D-Gluconylaminomethyl-4-hydroxyamino-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide methanesulfonate

$[\alpha]_D^{24}$ = -3.9° (c 0.21, 1N-HClaq.)

mp : 180-185°C (dec.)

NMR (DMSO-d_6, δ) : 0.74 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.88 (1H, m), 1.29 (1H, m), 1.37 (1H, m), 2.14 (1H, ddd, J=9, 9, 3Hz), 2.29-2.54 (2H, m), 2.32 (3H, s), 2.60 (3H, d, J=4.5Hz), 2.88 (1H, m), 3.07 (1H, dd, J=14, 12Hz), 3.22 (1H, dd, J=14, 4Hz), 3.41-3.64 (4H, m), 3.88-3.99 (2H, m), 4.70 (1H, ddd, J=12, 8, 4Hz), 7.12 (1H, dd, J=5, 5Hz),

7.90 (2x1H, d, J=6Hz), 7.93 (1H, q, J=4.5Hz), 8.42 (1H, d, J=8Hz), 8.75 (2x1H, br d, J=6Hz), 10.46 (1H, s)

HPLC : 3.7 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:H_2O:TFA = 10:90:0.05, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=558

Example 18

To a stirred suspension of N-[(2R,3R)-4-benzyloxyamino-3-ethoxycarbonylacetylaminomethyl-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide (243 mg) in methanol (5 ml) was added 1N aqueous sodium hydroxide solution (1.2 ml) at ambient temperature. The mixture was stirred at the same temperature for 4 hours. The solution was neutralized by dropwise addition of 1N-hydrochloric acid (1.2 ml). The precipitate was collected and washed with water to give N-[(2R,3R)-4-benzyloxyamino-3-carboxyacetylaminomethyl-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide (216 mg).

$[\alpha]_D^{23}$ = -38.3° (c 0.21, 1N-HClaq.)

mp : 246-250°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.77 (3H, d, J=7Hz), 0.80 (1H, m), 1.23 (1H, m), 1.37 (1H, m), 2.20 (1H, ddd, J=11, 9, 3Hz), 2.44 (1H, m), 2.55 (3H, d, J=5Hz), 2.62-2.91 (3H, m), 2.95 (1H, dd, J=14, 5Hz), 3.03 (1H, d, J=15Hz), 3.10 (1H, d, J=15Hz), 4.57 (1H, ddd, J=10, 8, 5Hz), 4.72 (1H, d, J=11Hz), 4.80 (1H, d, J=11Hz), 7.24 (2x1H, d, J=7Hz), 7.29-7.42 (5H, m), 7.77-7.93 (2H, m), 8.33 (1H, d, J=8Hz), 8.40 (2x1H, d, J=7Hz), 11.05 (1H, s)

HPLC : 5.3 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=556

Example 19-1)

N-[(2R,3R)-3-(N-tert-Butoxycarbonylglycyl)aminomethyl-4-hydroxyamino-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide (130 mg) was dissolved in 10% hydrogen chloride in methanol (5 ml). After the solution was stirred at ambient temperature for 40 minutes, the solvent was evaporated in vacuo. The obtained solid was triturated with ethyl acetate, collected and washed with ethyl acetate to give N-[(2R,3R)-3-glycylaminomethyl-4-hydroxyamino-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide dihydrochloride (86 mg) as a powder.

$[\alpha]_D^{24}$ = -23.5° (c 0.28, 1N-HClaq.)

mp : 250-255°C (dec.)

NMR (DMSO-d_6, δ) : 0.74 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.85 (1H, m), 1.26 (1H, m), 1.38 (1H, m), 1.95-2.15 (2H, m), 2.33 (1H, m), 2.62 (3H, d, J=5Hz), 2.68 (1H, m), 3.06 (1H, dd, J=13, 12Hz), 3.28 (1H, dd, J=13, 4Hz), 3.35-3.60 (2H, m), 4.77 (1H, ddd, J=12, 8, 4Hz), 7.98 (2x1H, d, J=7Hz), 8.02-8.20 (4H, m), 8.49 (1H, d, J=8Hz), 8.75 (2x1H, d, J=7Hz), 10.45 (1H, s)

HPLC : 3.3 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:H_2O:TFA = 10:90:0.05, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=437

Example 19-2)

N-{(2R,3R)-3-[(2S)-2-Amino-3-hydroxypropionyl]aminomethyl-4-hydroxyamino-2-isobutylsuccinyl}-L-4-pyridylalanine methylamide dihydrochloride was obtained in substantially the same manner as that of Example 19-1).

$[\alpha]_D^{24}$ = -17.8° (c 0.28, 1N-HClaq.)

mp : 236-243°C (dec.)

NMR (DMSO-d_6, δ) : 0.74 (3H, d, J=7Hz), 0.80 (3H, d,

J=7Hz), 0.84 (1H, m), 1.27 (1H, m), 1.36 (1H, m), 2.01 (1H, m), 2.20-2.48 (2H, m), 2.63 (3H, d, J=4.5Hz), 3.06 (1H, dd, J=13, 12Hz), 3.28 (1H, dd, J=13, 4Hz), 3.60 (1H, dd, J=11, 7Hz), 3.67 (1H, dd, J=11, 3Hz), 3.77 (1H, m), 4.79 (1H, ddd, J=12, 8, 4Hz), 7.97 (2x1H, d, J=6Hz), 8.07 (1H, q, J=4.5Hz), 8.15-8.28 (3H, m), 8.50 (1H, d, J=8Hz), 8.73 (2x1H, d, J=6Hz), 10.45 (1H, s)

HPLC : 3.1 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:H_2O:TFA = 10:90:0.05, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=467

Example 20-1)

N-[(2R,3R)-4-Benzyloxyamino-3-(2-hydroxyethoxy)carbonyl-aminomethyl-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide was obtained from N-[(2R,3R)-3-(2-acetoxyethoxy)-carbonylaminomethyl-4-benzyloxyamino-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide in substantially the same manner as that of Example 18.

$[\alpha]_D^{23}$ = -16.2° (c 0.21, 1N-HClaq.)

mp : 237-240°C (dec.)

NMR (DMSO-d_6, δ) : 0.65-0.88 (1H, m), 0.70 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 1.17-1.40 (2H, m), 2.14 (1H, m), 2.31-2.61 (2H, m), 2.55 (3H, d, J=4.5Hz), 2.70 (1H, m), 2.81 (1H, dd, J=14, 12Hz), 2.95 (1H, dd, J=14, 5Hz), 3.45-3.58 (2H, m), 3.81-3.98 (2H, m), 4.56 (1H, ddd, J=12, 8, 5Hz), 4.70 (1H, d, J=11Hz), 4.76 (1H, d, J=11Hz), 6.71 (1H, dd, J=6, 6Hz), 7.25 (2x1H, d, J=6Hz), 7.28-7.42 (5H, m), 7.86 (1H, q, J=4.5Hz), 8.36 (1H, d, J=8Hz), 8.39 (2x1H, d, J=6Hz), 10.95 (1H, s)

HPLC : 4.9 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=558

The following compounds were obtained in substantially the same manner as that of Example 20-1).

Example 20-2)

N-[(2R,3R)-4-Benzyloxyamino-3-hydroxyacetylaminomethyl-2-isobutylsuccinyl]-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -33.8° (c 0.22, 1N-HClaq.)

mp : 239-244°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.82 (1H, m), 1.26 (1H, m), 1.34 (1H, m), 2.23 (1H, ddd, J=9, 9, 4Hz), 2.41-2.53 (1H, m), 2.56 (3H, d, J=4.5Hz), 2.73 (1H, m), 2.38 (1H, dd, J=14, 11Hz), 2.90-3.03 (2H, m), 3.75 (2H, d, J=6Hz), 4.54 (1H, m), 4.71 (1H, d, J=11Hz), 4.78 (1H, d, J=11Hz), 5.45 (1H, t, J=6Hz), 7.21 (1H, m), 7.24 (2x1H, d, J=6Hz), 7.85 (1H, q, J=4.5Hz), 8.35-8.44 (3H, m), 11.09 (1H, s)

HPLC : 4.8 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=528

Example 20-3)

N-[(2R,3R)-4-Benzyloxyamino-3-hydroxyacetamidomethyl-2-isobutylsuccinyl]-L-3-pyridylalanine methylamide

$[\alpha]_D^{24}$ = -38.8° (c 0.24, 1N-HClaq.)

mp : 253-256°C (dec.)

NMR (DMSO-d_6, δ) : 0.71 (3H, d, J=7Hz), 0.79 (3H, d, J=7Hz), 0.82 (1H, m), 1.25 (1H, m), 1.33 (1H, m), 2.22 (1H, ddd, J=9, 9, 4Hz), 2.47 (1H, m), 2.54 (3H, d, J=4.5Hz), 2.65 (1H, ddd, J=13, 5, 4Hz), 2.82 (1H, dd, J=14, 11Hz), 2.94 (1H, dd, J=14, 6Hz), 3.75 (2H, d, J=6Hz), 4.50 (1H, m), 4.71 (1H,

d, J=11Hz), 4.77 (1H, d, J=11Hz), 5.43 (1H, t, J=6Hz), 7.19 (1H, dd, J=5, 5Hz), 7.23 (1H, dd, J=7.5, 5Hz), 7.30-7.42 (5H, m), 7.64 (1H, br d, J=7.5Hz), 7.84 (1H, q, J=4.5Hz), 8.30-8.40 (2H, m), 8.44 (1H, br s), 11.09 (1H, s)

HPLC : 4.9 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:H_2O:TFA = 25:75:0.05, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=528

Example 21-1)

N-[(2R,3R)-4-Benzyloxyamino-2-isobutyl-3-(methylcarbamoylacetylaminomethyl)succinyl]-L-4-pyridylalanine methylamide was obtained in substantially the same manner as that of Example 2-1).

$[\alpha]_D^{23}$ = -46.2° (c 0.21, 1N-HClaq.)

mp : 257-260°C (dec.)

NMR (DMSO-d_6, δ) : 0.70 (3H, d, J=7Hz), 0.73-0.87 (1H, m), 0.77 (3H, d, J=7Hz), 1.23 (1H, m), 1.36 (1H, m), 2.18 (1H, ddd, J=10, 9, 4Hz), 2.44 (1H, m), 2.55 (3H, d, J=5Hz), 2.58 (3H, d, J=5Hz), 2.63-2.89 (2H, m), 2.83 (1H, dd, J=14, 10Hz), 2.90-3.03 (1H, m), 2.97 (2H, s), 4.58 (1H, m), 4.70 (1H, d, J=11Hz), 4.80 (1H, d, J=11Hz), 7.25 (2x1H, d, J=7Hz), 7.28-7.42 (5H, m), 7.77-7.93 (3H, m), 8.33 (1H, d, J=8Hz), 8.40 (2x1H, d, J=6Hz), 11.02 (1H, br)

HPLC : 5.0 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=569

Example 21-2)

N-{(2R,3R)-4-Benzyloxyamino-2-isobutyl-3-[(3-methylcarbamoylmethyl)ureidomethyl]succinyl}-L-4-pyridylalanine

methylamide was obtained in substantially the same manner as that of Example 2-1).

$[\alpha]_D^{23}$ = -28.2° (c 0.23, 1N-HClaq.)

mp : 244-249°C (dec.)

NMR ($DMSO-d_6$, δ) : 0.69 (3H, d, J=6.5Hz), 0.75 (3H, d, J=6.5Hz), 0.80 (1H, m), 1.20 (1H, m), 1.34 (1H, m), 2.19 (1H, m), 2.40 (1H, m), 2.56 (3H, d, J=4.5Hz), 2.60 (3H, d, J=4.5Hz), 2.71 (2H, dd, J=6, 6Hz), 2.84 (1H, dd, J=14, 11Hz), 3.00 (1H, dd, J=14, 5Hz), 3.53 (1H, dd, J=17, 6Hz), 3.63 (1H, dd, J=17, 6Hz), 3.75 (2H, d, J=6Hz), 4.56 (1H, ddd, J=11, 8.5, 5Hz), 4.74 (1H, d, J=11Hz), 4.80 (1H, d, J=11Hz), 5.90 (1H, t, J=6Hz), 6.14 (1H, dd, J=6, 6Hz), 7.24 (2x1H, d, J=6Hz), 7.31-7.44 (5H, m), 7.72 (1H, q, J=4.5Hz), 7.84 (1H, q, J=4.5Hz), 8.25 (1H, d, J=8.5Hz), 8.40 (2x1H, d, J=6Hz), 11.05 (1H, s)

HPLC : 4.6 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 25:75, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=584

The following compounds were obtained in substantially the same manner as those of Examples 12-1) and 19-1).

<u>Example 22-1)</u>

N-{(2R,3R)-3-(2-Aminoethoxy)carbonylaminomethyl-4-hydroxyamino-2-isobutylsuccinyl}-L-4-pyridylalanine methylamide from N-{(2R,3R)-4-benzyloxyamino-3-(2-benzyloxycarbonylamino)ethoxycarbonylaminomethyl-2-isobutylsuccinyl}-L-4-pyridylalanine methylamide

$[\alpha]_D^{23}$ = -19.5° (c 0.25, 1N-HClaq.)

mp : 201-206°C (dec.)

NMR ($DMSO-d_6$, δ) : 0.73 (3H, d, J=7Hz), 0.79 (3H, d, J=7Hz), 0.86 (1H, m), 1.28 (1H, m), 1.38 (1H, m),

2.17 (1H, m), 2.43 (1H, m), 2.58 (3H, d, J=4.5Hz), 2.68-2.89 (3H, m), 2.95 (1H, dd, J=14, 4Hz), 3.20-3.70 (2H, m), 3.88 (2H, t, J=6Hz), 4.57 (1H, m), 6.52 (1H, m), 7.26 (2x1H, d, J=6Hz), 7.87 (1H, q, J=4.5Hz), 8.35 (1H, d, J=8Hz), 8.50 (2x1H, d, J=6Hz)

HPLC : 3.3 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=467

Example 22-2)

N-{(2R,3R)-4-Hydroxyamino-3-[(4S)-2-oxoimidazolidin-4-yl)carbonylaminomethyl-2-isobutylsuccinyl}-L-4-pyridylalanine methylamide methanesulfonate from N-{(2R,3R)-4-benzyloxyamino-3-[(4S)-3-benzyloxycarbonyl-2-oxoimidazolidin-4-yl]carbonylaminomethyl-2-isobutylsuccinyl}-L-4-pyridylalanine methylamide

$[\alpha]_D^{24}$ = -25.4° (c 0.33, 1N-HClaq.)

mp : 201-204°C (dec.)

NMR (DMSO-d_6, δ) : 0.73 (3H, d, J=7Hz), 0.78 (3H, d, J=7Hz), 0.85 (1H, m), 1.25 (1H, m), 1.37 (1H, m), 2.10 (1H, ddd, J=9, 9, 3Hz), 2.30 (3H, s), 2.32-2.52 (2H, m), 2.55-2.70 (1H, m), 2.60 (3H, d, J=5Hz), 3.05 (1H, dd, J=14, 12Hz), 3.13-3.28 (2H, m), 3.46 (1H, dd, J=10, 9Hz), 4.00 (1H, m), 4.73 (1H, m), 6.28 (1H, br), 7.48 (1H, dd, J=6, 6Hz), 7.88 (2x1H, d, J=6Hz), 7.93 (1H, q, J=5Hz), 8.41 (1H, d, J=8Hz), 8.72 (2x1H, d, J=6Hz), 10.43 (1H, s)

HPLC : 3.7 min. (Nucleosil 5C18, 4 mmϕ x 15 cm, MeCN:H_2O:TFA = 10:90:0.05, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=492

Example 23

To a stirred suspension of N-[(2R,3R)-4-hydroxyamino-2-isobutyl-3-(methanesulfonylaminomethyl)succinyl]-L-3-pyridylalanine methylamide (124 mg) in ethanol (1 ml) was added methanesulfonic acid (28 mg). The mixture was heated until a clear solution was obtained. The solution was allowed to cool to ambient temperature and diluted with ethyl acetate with stirring. The precipitate was collected and washed with ethyl acetate to give N-[(2R,3R)-4-hydroxyamino-2-isobutyl-3-(methanesulfonylaminomethyl)succinyl]-L-3-pyridylalanine methylamide methanesulfonate (142 mg) as a powder.

$[\alpha]_D^{23}$ = -12.4° (c 0.32, 1N-HClaq.)

mp : 140-146°C (dec.)

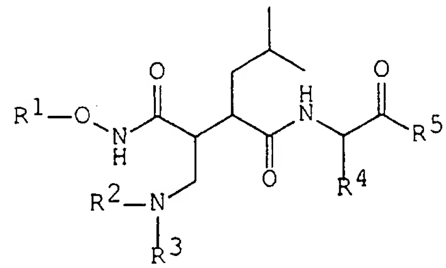
NMR (DMSO-d_6, δ) : 0.74 (3H, d, J=7Hz), 0.80 (3H, d, J=7Hz), 0.90 (1H, m), 1.29 (1H, m), 1.39 (1H, m), 2.13 (1H, ddd, J=9, 9, 3Hz), 2.23 (1H, ddd, J=13, 5, 4Hz), 2.32 (3H, s), 2.37 (1H, m), 2.58 (3H, d, J=5Hz), 2.80 (1H, m), 3.01 (1H, dd, J=14, 11Hz), 3.13 (1H, dd, J=14, 5Hz), 4.56 (1H, ddd, J=11, 8, 5Hz), 6.72 (1H, dd, J=6, 5Hz), 7.85-7.97 (2H, m), 8.35 (1H, d, J=8Hz), 8.40 (1H, d, J=7.5Hz), 8.75 (1H, d, J=5Hz), 8.80 (1H, s), 10.49 (1H, s)

HPLC : 4.1 min. (Nucleosil 5C18, 4 mmφ x 15 cm, MeCN:0.05% TFAaq. = 10:90, 260 nm, flow rate 1.0 ml/min., at R.T.)

MASS : M+H=458

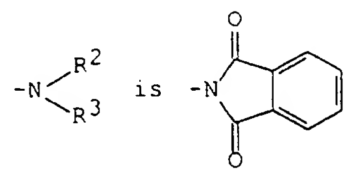
CLAIMS

1. A compound of the following formula :



in which R^1 is hydrogen or hydroxy-protective group,
R^2 is hydrogen or acyl,
R^3 is hydrogen or lower alkyl, or

the formula :



,

R^4 is heterocyclic(lower)alkyl, and
R^5 is lower alkoxy or lower alkylamino,
or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1, wherein
R^1 is hydrogen,
R^2 is hydrogen; oxamoyl; lower alkanoyl; lower alkanesulfonyl; lower alkoxycarbonyl; (C_3-C_7)cycloalkanecarbonyl; di(lower)alkylamino(lower)alkanoyl; lower alkylcarbamoyl; di(lower)alkylcarbamoyl; N-[(lower)alkylcarbamoyl(lower)alkyl]carbamoyl; C_6-C_{10} aroyl; C_6-C_{10} arenesulfonyl; C_6-C_{10} arylcarbamoyl; heterocyclic-carbonyl

optionally substituted by the group consisting of acyl, lower alkyl, hydroxy and oxo; heterocyclic-carbamoyl; (C_6-C_{10})aryloxy(lower)alkanoyl; heterocyclic(lower)alkanoyl; lower alkylcarbamoyl(lower)alkanoyl; carboxy(lower)alkanoyl; protected carboxy(lower)alkanoyl; hydroxy(lower)alkanoyl; protected hydroxy(lower)alkanoyl; lower alkoxy(lower)alkanoyl; lower alkoxy(lower)alkoxycarbonyl; amino(lower)alkoxycarbonyl; protected amino(lower)alkoxycarbonyl; lower alkoxycarbonyl(lower)alkylcarbamoyl; lower alkylsulfonyl(lower)alkanoyl; hydroxy(lower)alkoxycarbonyl; protected hydroxy(lower)alkoxycarbonyl; lower alkanoyl substituted by the group consisting of amino and hydroxy; lower alkanoyl substituted by the group consisting of protected amino and hydroxy; amino(lower)alkanoyl; or protected amino(lower)alkanoyl;

said heterocyclic groups being

unsaturated 3- to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),

saturated 3- to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 7- to 12-membered condensed heterocyclic group containing 1 to 4 nitrogen atom(s),

saturated 7- to 12-membered condensed heterocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 3- to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3

nitrogen atom(s),

saturated 3- to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),

unsaturated 7- to 12-membered condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),

unsaturated 3- to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

saturated 3- to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

unsaturated 7- to 12-membered condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

unsaturated 3- to 8-membered heteromonocyclic group containing an oxygen atom,

unsaturated 3- to 8-membered heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s),

unsaturated 7- to 12-membered condensed heterocyclic group containing 1 to 2 sulfur atom(s), or

unsaturated 7- to 12-membered condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), and

R^4 is heterocyclic(lower)alkyl,

said heterocyclic groups being

unsaturated 3- to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),

saturated 3- to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 7- to 12-membered condensed heterocyclic group containing 1 to 4 nitrogen

atom(s),

saturated 7- to 12-membered condensed heterocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 3- to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),

saturated 3- to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),

unsaturated 7- to 12-membered condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),

unsaturated 3- to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

saturated 3- to 8-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

unsaturated 7- to 12-membered condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s),

unsaturated 3- to 8-membered heteromonocyclic group containing an oxygen atom,

unsaturated 3- to 8-membered heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s),

unsaturated 7- to 12-membered condensed heterocyclic group containing 1 to 2 sulfur atom(s), or

unsaturated 7- to 12-membered condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s).

3. The compound of Claim 2, wherein

R^2 is hydrogen; oxamoyl; lower alkanoyl; lower alkanesulfonyl; lower alkoxycarbonyl; (C_3-C_7)cycloalkanecarbonyl; di(lower)alkylamino(lower)alkanoyl; lower alkylcarbamoyl; di(lower)alkylcarbamoyl; N-[(lower)alkylcarbamoyl(lower)alkyl]carbamoyl; C_6-C_{10} aroyl; C_6-C_{10} arenesulfonyl; C_6-C_{10} arylcarbamoyl; heterocyclic-carbonyl optionally substituted by the group consisting of C_6-C_{10} ar(lower)alkoxycarbonyl, lower alkyl, hydroxy and oxo, said heterocyclic group being

unsaturated 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),

saturated 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 9- or 10-membered bicyclic heterocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom, or

saturated 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom;

heterocyclic-carbamoyl, said heterocyclic group being

unsaturated 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),

saturated 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 9- or 10-membered bicyclic

heterocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom, or

saturated 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom;

(C_6-C_{10})aryloxy(lower)alkanoyl;

heterocyclic(lower)alkanoyl, said heterocyclic group being

unsaturated 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s)

saturated 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 9- or 10-membered bicyclic heterocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s), or

saturated 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s);

lower alkylcarbamoyl(lower)alkanoyl; carboxy(lower)alkanoyl; protected carboxy(lower)alkanoyl; hydroxy(lower)alkanoyl; protected hydroxy(lower)alkanoyl; lower alkoxy(lower)alkanoyl; lower alkoxy(lower)alkoxycarbonyl; amino(lower)alkoxycarbonyl; C_6-C_{10} ar(lower)alkoxycarbonylamino(lower)alkoxycarbonyl; lower alkoxycarbonyl(lower)alkylcarbamoyl;

lower alkylsulfonyl(lower)alkanoyl; hydroxy(lower)alkoxycarbonyl; protected hydroxy(lower)alkoxycarbonyl; lower alkanoyl substituted by the group consisting of amino and hydroxy; lower alkanoyl substituted by the group consisting of protected amino and hydroxy; amino(lower)alkanoyl; or protected amino(lower)alkanoyl; and

R^4 is heterocyclic(lower)alkyl, said heterocyclic group being

unsaturated 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),

saturated 5- or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 9- or 10-membered bicyclic heterocyclic group containing 1 to 4 nitrogen atom(s),

unsaturated 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s), or

saturated 5- or 6-membered heteromonocyclic group containing 1 to 2 oxygen atom(s).

4. The compound of Claim 3, wherein

R^2 is hydrogen; oxamoyl; lower alkanoyl; lower alkanesulfonyl; lower alkoxycarbonyl; (C_3-C_7)cycloalkanecarbonyl; di(lower)alkylamino(lower)alkanoyl; lower alkylcarbamoyl; di(lower)alkylcarbamoyl; N-[(lower)alkylcarbamoyl(lower)alkyl]carbamoyl; C_6-C_{10} aroyl; C_6-C_{10} arenesulfonyl; C_6-C_{10} arylcarbamoyl; heterocyclic-carbonyl optionally substituted by the group consisting of C_6-C_{10} ar(lower)alkoxycarbonyl, lower alkyl, hydroxy and oxo, said heterocyclic group being pyrrolyl, pyridyl, pyrazinyl, pyrrolidinyl,

imidazolidinyl, indolyl, isoindolyl, quinolyl, isoquinolyl, furyl, or oxolanyl;
pyridylcarbamoyl;
(C_6-C_{10})aryloxy(lower)alkanoyl;
heterocyclic(lower)alkanoyl, said heterocyclic group being
imidazolyl or pyridyl;
lower alkylcarbamoyl(lower)alkanoyl;
carboxy(lower)alkanoyl;
lower alkoxycarbonyl(lower)alkanoyl;
hydroxy(lower)alkanoyl;
lower alkanoyloxy(lower)alkanoyl;
lower alkoxy(lower)alkanoyl;
lower alkoxy(lower)alkoxycarbonyl;
amino(lower)alkoxycarbonyl; C_6-C_{10} ar(lower)-alkoxycarbonylamino(lower)alkoxycarbonyl;
lower alkoxycarbonyl(lower)alkylcarbamoyl;
lower alkylsulfonyl(lower)alkanoyl;
hydroxy(lower)alkoxycarbonyl;
lower alkanoyloxy(lower)alkoxycarbonyl;
lower alkanoyl substituted by the group consisting of amino and hydroxy; lower alkanoyl substituted by the group consisting of lower alkoxycarbonylamino and hydroxy; amino(lower)alkanoyl; lower alkanoylamino(lower)alkanoyl, or lower alkoxycarbonylamino(lower)alkanoyl; and
R^4 is pyridyl(lower)alkyl.

5. The compound of claim 4, wherein
R^2 is hydrogen;
oxamoyl;
C_1-C_6 alkanoyl optionally substituted by halogen;
C_1-C_4 alkanesulfonyl;
C_1-C_4 alkoxycarbonyl;
(C_3-C_7)cycloalkanecarbonyl;

di(C_1-C_4)alkylamino(C_1-C_4)alkanoyl;
C_1-C_4 alkylcarbamoyl;
di(C_1-C_4)alkylcarbamoyl;
N-[(C_1-C_4)alkylcarbamoyl(C_1-C_4)alkyl]carbamoyl;
benzoyl;
benzenesulfonyl;
phenylcarbamoyl;
pyrrolylcarbonyl;
pyridinecarbonyl optionally substituted by C_1-C_4 alkyl;
pyrazinylcarbonyl;
pyrrolidinylcarbonyl optionally substituted by oxo;
imidazolizinylcarbonyl optionally substituted by the group consisting of oxo phenyl(C_1-C_4)-alkoxycarbonyl;
quinolinecarbonyl optionally substituted by hydroxy;
indoylcarbonyl; isoindolylcarbonyl;
furoyl;
oxolanecarbonyl optionally substituted by oxo;
pyridylcarbamoyl;
phenoxy(C_1-C_4)alkanoyl;
imidazolyl(C_1-C_4)alkanoyl;
pyridyl(C_1-C_4)alkanoyl;
piperidinyl(C_1-C_4)alkanoyl;
C_1-C_4 alkylcarbamoyl(C_1-C_4)alkanoyl;
carboxy(C_1-C_4)alkanoyl;
C_1-C_4 alkoxycarbonyl(C_1-C_4)alkanoyl;
mono- or di- or tri- or tetra- or pentahydroxy-(C_1-C_6)alkanoyl;
C_1-C_4 alkanoyloxy(C_1-C_4)alkanoyl;
C_1-C_4 alkoxy(C_1-C_4)alkanoyl;
C_1-C_4 alkoxy$(C_1-C_4\ )$alkoxycarbonyl;
amino(C_1-C_4)alkoxycarbonyl;
phenyl(C_1-C_4)alkoxycarbonylamino(C_1-C_4)-

alkoxycarbonyl;

C_1-C_4 alkoxycarbonyl(C_1-C_4)alkylcarbamoyl;

C_1-C_4 alkylsulfonyl(C_1-C_4)alkanoyl;

hydroxy(C_1-C_4)alkoxycarbonyl;

C_1-C_4 alkanoyloxy(C_1-C_4)alkoxycarbonyl;

C_1-C_4 alkanoyl substituted by the group consisting of amino and hydroxy;

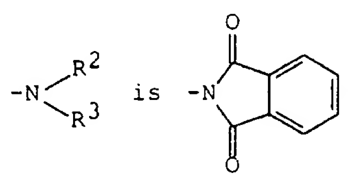
C_1-C_4 alkanoyl substituted by the group consisting of C_1-C_4 alkoxycarbonylamino and hydroxy;

amino(C_1-C_4)alkanoyl;

C_1-C_4 alkanoylamino(C_1-C_4)alkanoyl;

C_1-C_4 alkoxycarbonylamino(C_1-C_4)alkanoyl,

R^3 is hydrogen or C_1-C_4 alkyl, or the formula :

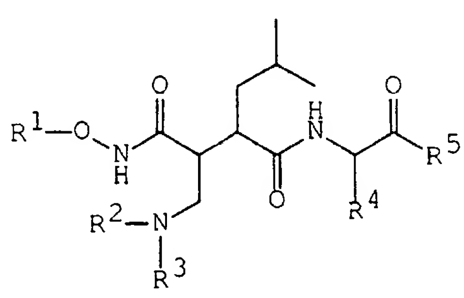


,

R^4 is pyridyl(C_1-C_4)alkyl, and

R^5 is C_1-C_4 alkoxy or C_1-C_4 alkylamino.

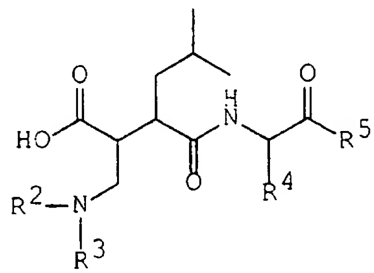
6. A process for the preparation of a compound of the formula :



(I)

or a salt thereof, which comprises

(a) reacting a compound of the formula :



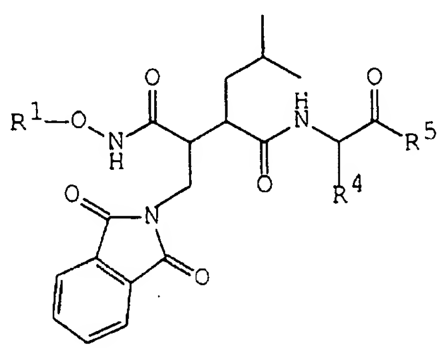
(II)

or a reactive derivative at the carboxy group, or a salt thereof with a compound of the formula :

$$R^1\text{-O-NH}_2 \qquad \text{(III)}$$

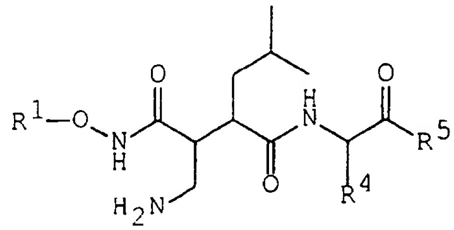
or a reactive derivative at the amino group, or a salt thereof, to give a compound of the formula (I) or a salt thereof; or

(b) subjecting a compound of the formula :



(I-a)

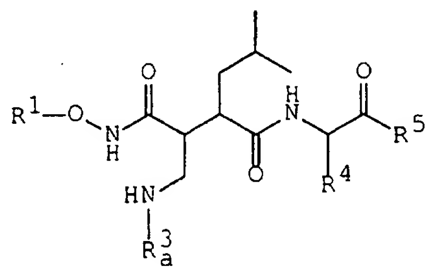
or a salt thereof to a removal reaction of the phthalimido moiety to give a compound of the formula :



(I-b)

or a salt thereof; or

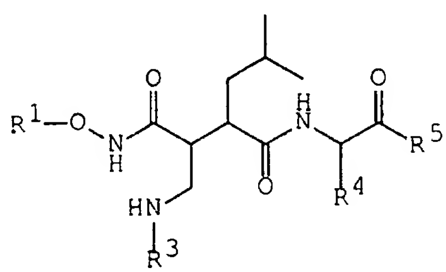
(c) alkylating the amino group of a compound of the above formula (I-b) or a salt thereof, to give a compound of the formula :



(I-c)

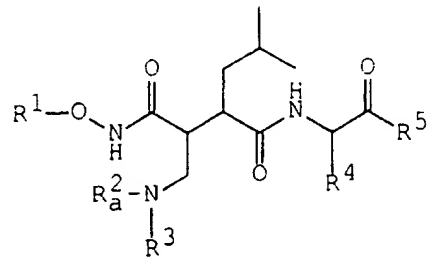
or a salt thereof; or

(d) acylating a compound of the formula :



(I-d)

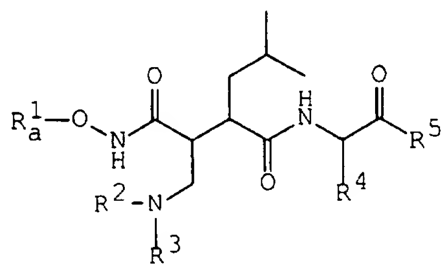
or a salt thereof to give a compound of the formula :



(I-e)

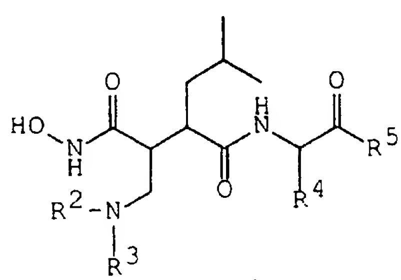
or a salt thereof; or

(e) subjecting a compound of the formula :



(I-f)

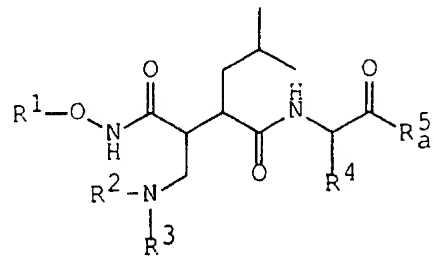
or a salt thereof to a removal reaction of the hydroxy-protective group to give a compound of the formula :



(I-g)

or a salt thereof; or

(f) reacting a compound of the formula :

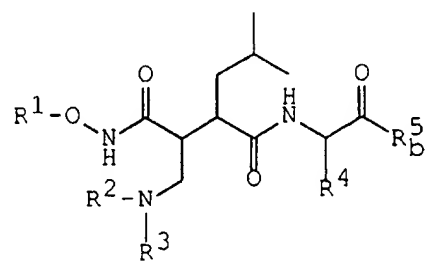


(I-h)

or a salt thereof, with a compound of the formula :

$$H-R^5_b \qquad (IV)$$

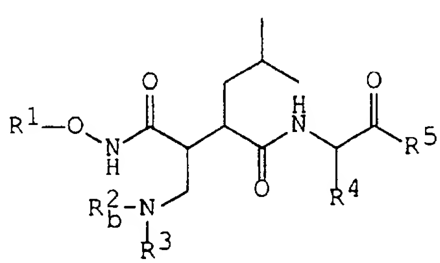
or its reactive derivative at the amino group, or a salt thereof, to give a compound of the formula :



(I-i)

or a salt thereof; or

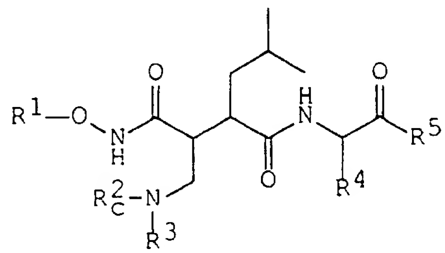
(g) subjecting a compound of the formula :



(I-j)

or a salt thereof, to a removal reaction of the carboxy-protective group on R^2_b, to give a compound of the

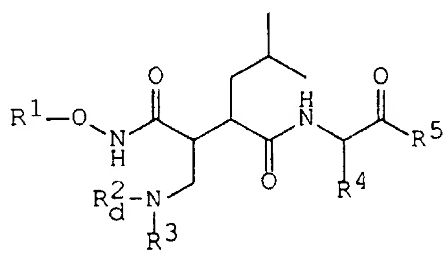
formula :



(I-k)

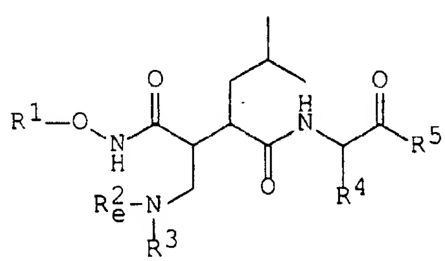
or a salt thereof; or

(h) subjecting a compound of the formula :



(I-l)

or a salt thereof, to a removal reaction of the amino-protective group on R_d^2, to give a compound of the formula :

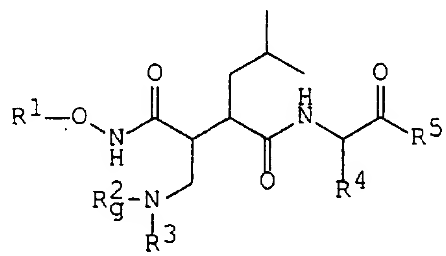


(I-m)

or a salt thereof; or

(i) subjecting a compound of the formula :

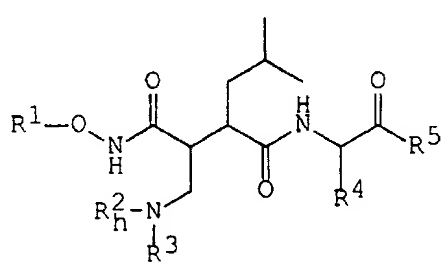
or a salt thereof, to a removal reaction of the hydroxy-protective group on R^2_f, to give a compound of the formula :



(I-o)

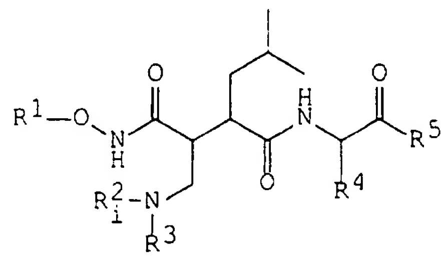
or a salt thereof; or

(j) reacting a compound of the formula :



(I-p)

or a salt thereof, with lower alkylamine, to give a compound of the formula :



(I-q)

or a salt thereof;

in which R^1, R^2, R^3, R^4 and R^5 are each as defined in Claim 1,

R^1_a is hydroxy-protective group,

R^2_a is acyl,

R^2_b is protected carboxy(lower)alkanoyl,

R^2_c is carboxy(lower)alkanoyl,

R^2_d is protected amino(lower)alkoxycarbonyl, protected amino(lower)alkanoyl, lower alkanoyl substituted by protected amino and hydroxy, or N-protected imidazolidinyl optionally substituted by oxo,

R^2_e is amino(lower)alkoxycarbonyl, amino(lower)alkanoyl, lower alkanoyl substituted by amino and hydroxy, or imidazolidinyl optionally substituted by oxo,

R^2_f is protected hydroxy(lower)alkoxycarbonyl, or protected hydroxy(lower)alkanoyl,

R^2_g is hydroxy(lower)alkoxycarbonyl, or hydroxy(lower)alkanoyl,

R^2_h is lower alkoxycarbonyl(lower)-alkylcarbamoyl or lower alkoxycarbonyl-lower alkanoyl,

R^2_i is lower alkylcarbamoyl(lower)-alkylcarbamoyl or lower alkylcarbamoyl

lower alkanoyl,

R_a^3 is lower alkyl,

R_a^5 is lower alkoxy, and

R_b^5 is lower alkylamino.

7. A pharmaceutical composition which comprises a compound of Claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

8. A process for preparing a pharmaceutical composition which comprises admixing a compound of Claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier or excipient.

9. A compound of Claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

10. A compound of Claim 1 or a pharmaceutically acceptable salt thereof for use as an inhibitor of MMP or TNF_α.

11. A use of a compound of Claim 1 or a pharmaceutically acceptable salt thereof for manufacturing a medicament for treating and/or preventing MMP or TNF_α mediated diseases.

12. A method for treating and/or preventing MMP or TNF_α mediated diseases which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

INTERNATIONAL SEARCH REPORT

Inter. ...nal Application No
PCT/JP 97/02004

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/55 C07D213/56 C07D213/81 C07D213/82 C07D401/12
C07D405/12 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 096, no. 006, 28 June 1996 & JP 08 053403 A (FUJISAWA PHARMACEUT CO LTD), 27 February 1996, see abstract	1-12
Y	WO 95 19965 A (GLYCOMED INC) 27 July 1995 see claims; example 20	1-12
Y	WO 95 19956 A (BRITISH BIOTECH PHARM ;BECKETT RAYMOND PAUL (GB); WHITTAKER MARK () 27 July 1995 see claims; example 37	1-12
A	WO 93 24449 A (CELLTECH LTD ;PORTER JOHN ROBERT (GB); MORPHY JOHN RICHARD (GB); M) 9 December 1993 see the whole document	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
17 September 1997	26.09.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Bosma, P

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 97/02004

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 12
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 97/02004

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9519965 A	27-07-95	AU 1604995 A	08-08-95
		CA 2158760 A	27-07-95
		EP 0690841 A	10-01-96
		JP 9501183 T	04-02-97
WO 9519956 A	27-07-95	AU 1459795 A	08-08-95
		CA 2181570 A	27-07-95
		CN 1138851 A	25-12-96
		DE 19581347 T	05-12-96
		EP 0740652 A	06-11-96
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		ZA 9500480 A	07-02-96
WO 9324449 A	09-12-93	AU 4341493 A	30-12-93
		CA 2114622 A	09-12-93
		EP 0605682 A	13-07-94
		JP 6509814 T	02-11-94
		US 5569665 A	29-10-96